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VEGF-C. Additionally, patients with lower levels of VEGF-C showed higher skin sodium storage after dialysis than those with higher VEGF-C levels [13].

Serum Osmolality

Despite the significant differences in the composition of the various body water compartments, under equilibrium conditions, there is electroneutrality and tonicity or osmolality, i.e., the sum of all osmotically active particles, is equal in all body water compartments. Under normal conditions, the serum osmolality is 286 ± 4 mosm/kg water. Because sodium is the major cation in the ECW, osmolality can be closely estimated by the formula:

$$\text{Serum osmolality} \approx 2 \times [\text{serum sodium concentration}] \tag{1}$$

A reflection coefficient of 1.0 indicates a totally non-permeant solute, while freely permeable molecules have a reflection coefficient of zero. The reflection coefficient for urea is approximately 0.4. Similarly, in the absence of insulin, the reflection coefficient for glucose is 0.5. When there is a pathological elevation in the serum urea nitrogen, e.g., acute kidney injury (AKI), or glucose concentration, e.g., diabetic ketoacidosis, these solutes will contribute to osmolality, albeit less effectively than sodium. Therefore, the following formula should be used to more accurately calculate serum osmolality:

$$\begin{aligned} \text{Serum osmolality} =\ & 2 \times [\text{serum sodium concentration}] \\ & + [\text{serum urea nitrogen}]/2.8 \\ & + [\text{serum glucose concentration}]/18 \end{aligned} \tag{2}$$

This formula is based on the molecular weights of urea nitrogen (28 Da) and glucose (180 Da) and the standard practice of reporting the serum concentrations as mg/100 ml. The calculated serum osmolality is normally within 1–2 % of the value obtained by direct osmometry in clinical chemistry laboratories. If the calculated serum osmolality is significantly lower than the value obtained by measurement with an osmometer, there is an "osmolal gap" and reflects the accumulation of unmeasured osmoles. Clinically relevant examples are the organic solutes that are produced after an ingestion of ethanol or ethylene glycol (antifreeze) [14, 15].

Maintenance Sodium and Water Requirements

Sodium

The total body sodium content in adults is approximately 80 mmol/kg of fat-free body weight. This proportion is higher in newborns, infants, and young children. Sodium is an essential dietary component in newborns that is required for normal growth, especially in very low-birth-weight infants. In adults, 30–50 % of sodium is contained in the skeleton. Because this proportion is smaller in infants, a positive sodium balance is required to build the skeleton and promote adequate growth [16]. Sodium stimulates cell growth and proliferation, possibly through the Na+ -H+ antiporter-mediated alkalinization of the cell interior. It causes protein synthesis by promoting nitrogen retention, thereby increasing muscle mass, and is necessary for proper neural development [17]. The growth-permissive role of sodium has been studied in animal models, which demonstrate that deprivation of NaCl results in a reduction in weight, height, muscle mass, and brain protein, RNA, and lipid content [18]. This effect is independent of the protein or calorie content of the diet. Interestingly, in contrast to chronic potassium deficiency induced by diuretics, compromised sodium intake does not cause structural damage to the kidney [19]. Although sodium supplementation restored the rate of growth to normal and reversed the brain abnormalities, it was not possible for these animals to catch up to the healthy controls [20]. The impact of sodium depletion has also been studied in children with salt-wasting renal diseases and in premature infants, both of which are particularly vulnerable

Table 1 Mean daily sodium intake and recommended amounts

Age group (years)	Actual sodium intake (g/day)	Recommended sodium intake (g/day)
1–5	4	2
6–10	6	4
11–20	8	5

to hyponatremia. In these cases, salt supplementation is necessary to promote normal growth and cognitive development [21].

Balance studies indicate that the daily sodium requirement is 2–3 mmol/kg body weight. This quantity is nearly two to threefold higher in term and very low-birth-weight premature infants [22]. This reflects the immaturity in renal tubular function coupled with the increased need for sodium to achieve the high rate of growth during early life. It will be exaggerated by intrinsic (diarrhea, increased losses via chronic peritoneal dialysis, genetic defect in tubular sodium transport) or exogenous (administration of diuretics) factors that promote sodium loss. In most developed countries, the daily sodium intake in childhood is in excess of the amount needed to promote growth or maintain body function. Table 1 summarizes the difference between actual sodium intake and current recommendations in young children and adolescents.

There has been extensive discussion about the daily sodium intake that yields optimal health in adults. An emerging consensus is that a daily salt intake in the range of 3–6 g is desirable to prevent hypertension and minimize cardiovascular morbidity and mortality [23–25]. A J curve, with extremely low or high sodium intake leading to worsening cardiovascular outcomes, appears to define the relationship in adults. This recommendation is based on large international cohort studies with extended follow-up, accurate assessment of sodium intake, and detailed characterization of the clinical outcomes. It is worth noting that even in adults with nondiabetic chronic kidney disease (CKD), reducing daily salt intake to below the 3–6 g range is not associated with improved renal or cardiovascular outcomes [26]. There are no comparable studies in pediatric patients who

do or do not have CKD. Therefore, it is not possible to define a daily sodium intake during childhood that will prevent cardiovascular and renal disease in adulthood.

Under normal circumstances, the principal anion that accompanies sodium is chloride. The identity of the anion that accompanies sodium and a variety of other dietary constituents impacts on the adverse consequences of excessive sodium intake such as hypertension [27]. In certain disease states such as renal tubular acidosis, metabolic acidosis associated with CKD, or urolithiasis, it may be advisable to provide a portion of the daily sodium requirement as the bicarbonate or the citrate salt.

Water

The daily requirement for water is traditionally expressed as ml per metabolic kg [28]. However, in clinical practice, this is a very cumbersome and impractical method and all calculations are based on body weight or body surface area (BSA). There are three methods that are currently utilized to estimate the daily fluid requirement. The first is a direct extension of the use of metabolic kilogram and utilizes the following formula:

1. Daily water requirement = 100 ml/kg for a child weighing less than 10 kg + 50 ml/kg for each additional kg up to 20 kg + 20 ml/kg for each kg in excess of 20 kg

   The second method is based on BSA and utilizes the following formula:

2. Daily water requirement = 1500 ml/m^2 BSA

   The last method is a refinement of the second and utilizes the following formula:

3. Daily water requirement = Urine output + insensible water losses

Based on clinical experience, under normal circumstances, urine output is approximately 1,000 ml/m^2 per day and insensible losses amount to 500 ml/m^2 per day.

Example: For a child weighing 30 kg and 123 cm in height with a BSA of 1.0 m^2, according to the first method, the daily water requirement is

1,700 ml, while the second method yields 1,500 ml per day. The first method is easier to apply, but it tends to overestimate the water requirement as body weight increases. The third method is the most precise and should be applied in more complicated circumstances such as the patient in the intensive care unit with oliguria secondary to AKI or the child with increased insensible losses, e.g., diarrhea, increased ambient temperature, tachypnea, burns, or cystic fibrosis [29]. In addition to the daily energy requirement and insensible losses that are represented in the formulas, the amount of water excreted by the kidney on a daily basis is dependent upon the solute load. Because urine has a minimum osmolality, approximately 50 mosm/kg H_2O, even in the absence of arginine vasopressin (AVP), increased dietary intake of solute will result in a larger obligatory urine volume to accommodate the larger solute load [30, 31].

Provision of adequate water intake is especially important in select medical conditions such as urolithiasis and CKD where higher water intake can prevent disease recurrence or progression, respectively [32].
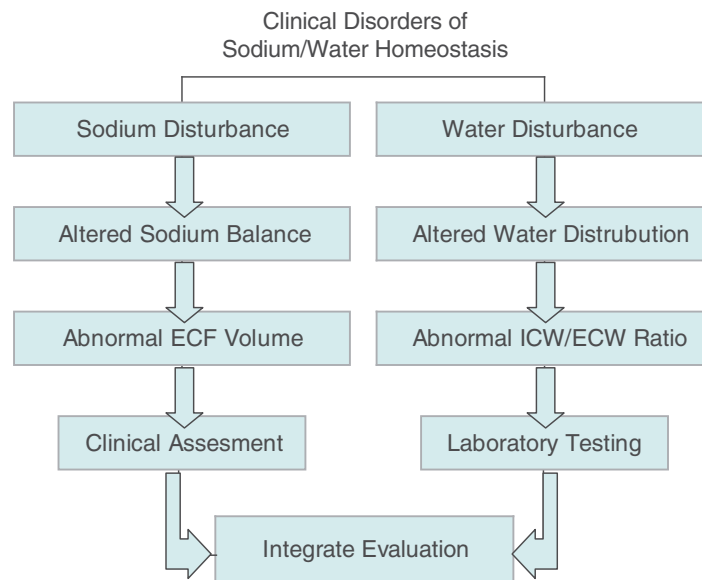
The daily sodium and water requirement are generally provided enterally. Intravenous administration of fluids and electrolytes should be resorted to only under clinical circumstances that interfere with normal feeding such a persistent vomiting, gastrointestinal tract surgery, or states of altered consciousness.

The choice of parenteral fluid for maintenance therapy in children has long been debated in the literature and by clinicians. Holliday and Segar developed early guidelines based on a linkage between metabolic needs and fluid requirements in healthy children. They suggested that a hypotonic maintenance solution containing 0.2 % saline in 5 % dextrose water should be administered to sick children [33]. This guideline has been repeated in several recent reports [34–36]. Since then, many nephrologists have criticized this recommendation claiming that the Holliday and Segar guidelines were developed based on the study of healthy children. They assert that it does not apply to children with acute illness who often have reduced energy expenditure and lower levels

of sensible and insensible water loss. Additionally, acutely ill children often present with overproduction of AVP, which causes free water retention and renders the patient vulnerable to hyponatremia [37]. Adding hypotonic solution in the setting of inappropriate AVP secretion may place the child at even greater risk of serious complications of low serum sodium including headache, nausea, vomiting, muscle cramps, depressed reflexes, disorientation, seizures, respiratory arrest, and cerebral edema, which can lead to permanent brain damage and death [38]. Children are at even greater risk of developing neurological symptoms from hyponatremia because the size of their brain relative to their skull is greater than adults. Opponents of the use of hypotonic maintenance fluids have documented the occurrence of hyponatremia and neurological complications in hospitalized children who receive these fluids parenterally [37, 39]. To prevent cerebral edema and neurological consequences of hyponatremia, they advocate routine administration of isotonic saline (0.9 % NaCl), with or without dextrose, to all pediatric patients who require intravenous maintenance fluids [40]. Moritz and Ayus report more than 50 cases of neurologic damage and death from 1993 to 2003 as a result of iatrogenic hyponatremia due to administration of hypotonic maintenance fluid [37]. In large randomized control trials of critically ill and postoperative pediatric patients, Choong et al. [41, 42] support this view by demonstrating that the use of hypotonic parenteral maintenance solution results in significantly increased risk of hyponatremia as compared to isotonic fluids.

In a meta-analysis of randomized control trials, hypotonic maintenance fluids were associated with an increased risk of hyponatremia in ICU and postoperative patients [43]. Opponents to isotonic saline point to the risk of hypernatremia with isotonic solutions, yet results from Choong et al. suggest that isotonic maintenance fluids do not result in increased risk for hypernatremia [41, 42]. Several groups in the UK, Canada, and the USA, including the Institute for Safe Medication Practices, have warned against the use of hypotonic saline in the pediatric population. This issue will require well-designed interventional

Fig. 2 This scheme illustrates the importance of independent assessment of sodium and water handling in managing patients with clinical disorders of sodium-water homeostasis

Clinical Disorders of
Sodium/Water Homeostasis

| Sodium Disturbance | Water Disturbance |

| Altered Sodium Balance | Altered Water Distrubution |

| Abnormal ECF Volume | Abnormal ICW/ECW Ratio |

| Clinical Assesment | Laboratory Testing |

Integrate Evaluation

studies to supplement practice guidelines [44]. Finally, it is worth noting that in a prospective, open-label pilot study in 760 adults, implementation of a strategy to restrict chloride content of intravenous maintenance fluids resulted in a reduced incidence of AKI and the need for renal replacement therapy [45]. The impact of chloride-containing solutions on kidney function in pediatric patients has not been studied. In the interim, it is important to emphasize that in the face of clinically significant acute ECW contraction, there is universal agreement that isotonic fluids are necessary to effectively replete the intravascular compartment. Careful clinical and laboratory monitoring is key to ensuring good outcomes in all children who are given maintenance fluids and electrolytes parenterally.

Distinct Roles of Sodium and Water in Body Fluid Homeostasis

Sodium and water are inextricably linked in the determination of the serum sodium concentration. However, it is critical to recognize that sodium and water serve two distinct functions within the body. Sodium is instrumental in the maintenance of the size of the ECF space and the vascular perfusion compartment, while water is critical to the maintenance of the size of individual cells.

The regulation of sodium and water homeostasis represents two distinct processes with discrete sensing and effector mechanisms. Although these systems overlap, from a physiological and clinical perspective, a complete understanding of body fluids and electrolytes mandates separate evaluation of sodium and water (Fig. 2).

Because sodium is the principal cation in the ECW compartment, disturbances in total body sodium content are reflected by expansion or contraction of this space. Adequacy of the ECW compartment is essential to maintain the intravascular space and sustain perfusion of vital organs. In terrestrial mammals living in an environment where ECW volume depletion is a constant threat, the kidney is designed for maximal sodium reabsorption as the default mode unless physiological signals instruct it to respond otherwise.

The primary step in the pathogenesis of disturbances in ECW compartment size is a perturbation in sodium balance. When total body water and sodium content are within the normal range, the net sodium balance is zero and the daily intake of sodium is matched by losses in the urine, stool, and insensible losses. Provided kidney function is normal, the daily dietary sodium intake can be as low as 0.1 mmol/kg or in excess of 10 mmol/kg without any derangement in ECF compartment size. If the alterations in diet are not abrupt, then sodium balance is maintained, even when kidney

Table 2 Clinical diseases of sodium and water homeostasis: relationship between ECW size and tonicity

Tonicity ECW volume	Low	Normal	High
Low	Addison's disease	Isotonic diarrheal	Hypertonic diarrheal
	Salmonella diarrhea	Dehydration	Dehydration
	Mannitol infusion		Diabetes insipidus
Normal	SIADH	No disease	Acute sodium bicarbonate infusion
High	Acute renal failure	Nephrotic syndrome	Salt intoxication
	Nephrotic syndrome		Salt-water drowning
	Cirrhosis		
	Congestive heart		
	Failure		

function is markedly impaired [46]. In contrast, if the daily input of sodium exceeds losses, there is expansion of the ECF space with edema, while if the input does not match the daily losses, there will be symptoms and signs related to ECW space contraction. These disturbances are not associated with any obligatory parallel changes in the serum sodium concentration (Table 2).

The determination of ECW compartment size and adequacy has generally been based on a clinical assessment (see below). Recent advances have highlighted new technological methods to measure this space that may facilitate this evaluation and provide greater accuracy and validity. Bioelectrical impedance is an emerging technique for the measurement of body fluid content. It is an easy, affordable, and noninvasive method and potentially has great utility in many clinical areas. This tool applies an electrical current of various frequencies to measure the reactance and resistance of the space between electrodes placed on the skin. The reactance value is proportional to body mass and the resistance is inversely related to total body water (TBW) [47]. The correlation between bioimpedance analysis and TBW is strong as assessed by measurements made by deuterium dilution [48]. Fluid overload often indicates worsening disease severity in many clinical conditions including CKD, heart failure, and liver cirrhosis. As such, a reliable and efficient tool for measuring volume status is important in the management of these diseases [47]. Measurement of ECW fluid content is particularly important in patients undergoing dialysis. Blood pressure regulation in these individuals has proven difficult and abnormalities, including both hypotension and hypertension, are common. Bioimpedance has been established as a useful tool in monitoring the body fluid content of patients on dialysis and yields important information about their volume status, which can be used to reduce the cardiovascular risks associated with chronic renal replacement therapy [49].

Water homeostasis is a prerequisite for the normal distribution of fluid between the ICW and ECW compartments. Cell function is dependent on stabilization of cell volume in order to keep the cytosolic concentration of enzymes, cofactors, and ions at the appropriate level and to prevent molecular crowding. Perturbations in water balance result in fluctuations in serum osmolality. Because cell membranes permit free movement of water down its osmolal gradient, this causes obligatory shifts in water between the cell and the ECW space. Any disorder that alters the 2:1 ratio of water volume in the ICW/ECW spaces will be reflected by changes in cell size and subsequent cellular dysfunction. Under hypoosmolal conditions, water will move from the intravascular compartment into the cell, causing relative or absolute cell volume expansion. Conversely, if the serum osmolality is elevated, water will exit from the cell to the ECW space resulting in absolute or relative cellular contraction [50].

Disturbances in cell function related to abnormalities in cell size are most prominent in cerebral cells for two reasons. First, the blood-brain barrier limits the movement of solute between the ICW and ECW compartments while permitting unrestricted flow of water down an osmolal gradient [51]. Second, the brain is contained within the skull, which is a closed, noncompliant space, and is tethered to the cranial vault by bridging blood vessels, which limits its tolerance of cell swelling or contraction.

Thus, alterations in water balance and serum osmolality are dominated by clinical findings of central nervous system dysfunction, including lethargy, seizures, and coma [50].

In the same way that disturbances in sodium balance do not necessarily predict specific abnormalities in serum sodium concentration, the presence of a disturbance in water balance and serum osmolality is not linked to a specific abnormality in the ECW compartment size. The independent nature of disturbances in sodium and water balance is illustrated in Table 2. Alterations in ECW size can occur in patients with hypotonicity, isotonicity, or hypertonicity. Similarly, each alteration in serum osmolality can develop in patients with contraction or expansion of the ECW compartment.

The presence of disturbances in sodium and water homeostasis must be addressed separately in the clinical evaluation of patients with derangements in ECF volume or tonicity. This assessment must be integrated to obtain a comprehensive view of what is abnormal and determine how to effectively restore sodium and water homeostasis with minimal side effects (Fig. 2).

Sensor Mechanisms: Sodium and Water

For both sodium and water homeostasis, the sensor mechanisms that maintain the equilibrium state are primarily designed to be responsive to the consequences of abnormalities in sodium or water balance, i.e., changes in ECW and cell size, respectively, rather than measuring the primary variable. In this regard, they differ from the acid-base sensor that is directly responsive to changes in pH [52]. They operate using negative feedback loops in which deviations from normal are detected, counter-regulatory mechanisms are activated that antagonize the initiating event, and the system is restored to the normal state.

Sodium

The net sodium deficit is detected as a decrease in ECW space size, while the net sodium excess is perceived as an obligatory expansion of the ECW space. These receptors in the venous (low-pressure) and arterial (high-pressure) circulation, which are influenced by the filling pressure within the circulation, are called baroreceptors or mechanoreceptors. These signals are supplemented in certain instances by chemoreceptors that respond directly to changes in the serum sodium concentration and trigger adaptive modifications in renal sodium handling. These receptors may effect change by altering nervous system activity or by activating upstream promoter elements and stimulating the expression of relevant genes [53].

Atrial receptors: Within the right atrium, sensors possess the distensibility and compliance needed to detect alterations in intrathoracic blood volume provoked by increasing negative intrathoracic pressure or head-out water immersion. Both of these maneuvers, which increase the central blood volume and raise central venous and right atrial pressures, are followed by a brisk natriuresis and diuresis [54]. These relative changes are triggered even in the absence of a concomitant change in the total ECW space size. Neural receptors that respond to mechanical stretch or changes in right or left atrial pressure convey the signal via the vagus nerve [54, 55].

Hepatic receptors: The enhanced renal sodium excretion triggered by saline infusions directly into the hepatic vein versus the systemic circulation suggests that there are low-pressure sensors within the portal vein or hepatic vasculature. The hepatic responses to changes in sodium balance have been divided into two categories [56]. The "hepatorenal reflex" involves direct activation of sodium chemoreceptors and mechanoreceptors in the hepatoportal region, via the hepatic nerve, and causes a reflex decrease in renal nerve activity. The "hepatointestinal reflex" utilizes chemoreceptors to respond to changes in sodium concentration and modulate intestinal absorption of sodium via signals conveyed along the vagus nerve. Activation of these hepatic volume sensors may contribute to the sodium retention and edema states that develop secondary to chronic liver disease and cirrhosis with the associated intrahepatic hypertension.

Pulmonary receptors: There may also be pressure sensors within the pulmonary circulation that

are activated by changes in pulmonary perfusion or mean airway pressure [57]. The receptors in the lung may be located in the interstitial spaces and influence the physical forces that modulate paracellular absorption of sodium and water. They resemble receptors in the renal interstitium that also influence paracellular absorption of fluid and solutes along the nephron, especially in the proximal tubule segment [58].

Carotid arch receptors: There are also volume-dependent sensors on the high-pressure arterial side of the circulation including the carotid arch, the brain, and the renal circulation. Thus, occlusion of the carotid leads to increased sympathetic nervous system activity and alterations in renal sodium handling [55]. The responsiveness of the carotid arch receptors may be modulated by chronic changes in ECF volume. For example, a head-down bed position and a high salt diet blunt carotid baroreceptor activity [59].

Cerebral receptors: Increases in the sodium concentration of the CSF or brain arterial plasma promote renal sodium excretion [60]. Lesions in discrete anatomic areas of the brain such as the anteroventral third ventricle alter renal sodium reabsorption, confirming that there are central mechanisms of sensing changes in sodium balance and ECF volume. Derangements in the sensing system within the brain in patients with long-standing central nervous system diseases may contribute to the cerebral salt-wasting syndrome. Intracerebral expression of angiotensin-converting enzyme isoforms contributes to peripheral sodium and water handling [61].

If arterial sensors perceive underfilling of the vascular space, this activates counter-regulatory mechanisms to restore the ECW compartment size even if the receptors in the venous system detect adequate or even overfilling of the venous tree. This implies that despite normal or even excess total body sodium and net positive sodium balance, there are conditions in which the body perceives an inadequate circulating plasma volume. This has given rise to the notion of the "effective" intravascular volume, a concept that is applicable in the edema states such as congestive heart failure, cirrhosis, and nephrotic syndrome [62]. For example, in patients with cardiac pump failure,

perceived underfilling of the arterial tree may occur despite significant venous distention [40]. Similarly, women who develop edema during pregnancy may have primary peripheral vasodilatation and excess total body sodium [62, 63].

Water

The receptors that are responsible for regulating water homeostasis are primarily osmoreceptors and are sensitive to alterations in cell size [63, 64]. These osmoresponsive cells are located in the circumventricular organs and anterolateral regions of the hypothalamus, adjacent to but distinct from the supraoptic nuclei. They shrink or swell in response to increases or decreases in plasma tonicity and this change in cell size triggers the release of AVP and/or the sensation of thirst. The anatomic configuration of these cells enables them to be exposed to circulating peptides that are involved in water homeostasis.

AVP: AVP is a peptide containing nine amino acids and has a molecular weight of 1,099 Da. It is synthesized by magnocellular neurons in the hypothalamus, transported down the axon, and stored in the posterior pituitary in conjunction with larger proteins, called neurophysins [65]. The gene for AVP is located on chromosome 20 and has a cAMP response element in the promoter region. Prolonged stimulation of AVP release leads to upregulation of the AVP gene; however, the synthesis does not keep up with the need for the peptide because pituitary levels of AVP are usually depleted in states such as chronic salt loading and hypernatremia [66].

The principle solute that provokes the release of AVP is sodium. Infusion of sodium chloride to increase plasma osmolality results in increased secretion of AVP in the absence of parallel changes in ECW volume. This underscores the primary role of plasma osmolality per se in stimulating AVP release [64]. Mannitol, an exogenous solute that is used in clinical practice to treat increased intracranial pressure, is nearly as effective as sodium in stimulating AVP release. Urea and glucose are less than 50 % as effective as sodium in provoking AVP secretion because

they are more permeable than sodium and cause less pronounced changes in osmoreceptor cell volume. However, in disease states such as AKI or diabetic ketoacidosis, in which urea or glucose, respectively, acts as osmotically active molecules or following the exogenous administration of mannitol, these solutes also stimulate increases in AVP release. There is coupling between mechanical changes in membrane structure and hormone release. However, the exact mechanism and the neurotransmitters that mediate the actions of the osmoreceptors on the cells of the posterior pituitary have not been identified.

A variety of non-osmotic stimuli to AVP release may contribute to water handling in various disease states [64, 65]. Vomiting and acute hypoglycemia promote AVP release by neural-hormonal pathways that are not well defined. Stress associated with pain or emotional anxiety, physical exertion, high body temperature, acute hypoxia, and acute hypercapnia are other conditions that lead to increased secretion of AVP in the absence of a primary disturbance in water balance. Numerous drugs directly influence the hypothalamic release of AVP including carbamazepine, cyclophosphamide, and vincristine. Finally, hemodynamic changes arising from primary alterations in sodium balance and the ECW space can trigger AVP release. If the ECW volume disturbance is mild, then the stimulation of AVP release is modest. However, in the face of severe ECW volume contraction, there is marked secretion of AVP. Under these circumstances, the imperative to protect the effective circulating blood volume takes precedence over the need to maintain plasma osmolality and ECW volume is restored at the expense of hypoosmolality. This clinical observation indicates the intellectual attempts to separate sodium and water homeostatic mechanisms; these two factors are closely linked in vivo and there can be significant overlap in sensor and effector mechanisms in the regulation of ECW and ICW compartment size. Table 3 summarizes the factors that modulate AVP release.

In addition to AVP release, the osmoreceptor cells also respond to the changes in serum osmolality in an independent manner to stimulate thirst and increase drinking [67]. The stimuli for thirst

Table 3 Factors that increase AVP release

| ↑Plasma osmolality |
| Hemodynamic |
| ↓Blood volume |
| ↓Blood pressure |
| Emesis |
| Hypoglycemia |
| Stress |
| Elevated body temperature |
| Angiotensin II |
| Hypoxia |
| Hypercapnia |
| Drugs |

are generally the same as those for AVP release, with hypernatremia being the most potent trigger. The osmotic threshold for thirst in humans appears to be higher than for AVP secretion, namely, 295 mosm/kg. The sensing mechanism that leads to this increase in water intake is even more obscure than that for AVP release. It is likely that changes in ECW volume are also involved in this process because angiotensin II, which rises in states of ECW volume contraction, is a potent dipsogen [68]. Recent studies suggest that the day-to-day regulation of thirst by osmoreceptors is under the control of dopamine-mu opioid neurotransmitters in the brain, while angiotensin II may be activated under more stressful conditions.

Efferent Mechanisms: Sodium and Water

The efferent mechanisms involved in maintaining sodium and water balance include the neural and endocrine-humoral systems. There often is an overlap in the action of these effectors, with an individual effector having distinctive effects on both sodium and water balance.

Sodium

Renin-angiotensin-aldosterone axis: The major components of this system – renin, angiotensinogen, and angiotensin-converting enzyme (ACE) – are found within the kidney

and the vasculature of most organs. These elements are linked in a large feedback loop involving the liver, kidney, and lung as well as smaller loops within individual organs. This accounts for the often disparate data about plasma renin activity (PRA) and the expression of individual components within the kidney during disturbances in ECW compartment size.

Angiotensin II is the major signal generated by this axis [69]. There are two distinct forms of ACE and the ACE2 isoform may metabolize angiotensin II to non-pressor breakdown products that react with specific receptors and that are less likely to promote the development of hypertension [70]. This introduces another layer of complexity in the regulation of sodium balance by the renin-angiotensin axis. Angiotensin II interacts with two different receptors, and most of its biological activity is mediated by the angiotensin type 1 (AT1) receptor. The AT2 receptor is more prominently expressed in the fetal kidney; however, interaction of angiotensin II with the AT2 receptor postnatally stimulates the release of molecules such as nitric oxide that counteract the primary action of the peptide [71]. In addition, angiotensin I can be processed to the heptapeptide angiotensin 1-7, which interacts with a separate mas receptor and modulates the biological effects of angiotensin II [70]. More research is needed to elucidate the role of alternate forms of angiotensin such as angiotensin 1-7 on sodium and water balance in children.

The best-known effects of angiotensin II include peripheral vasoconstriction to preserve organ perfusion and stimulation of adrenal synthesis of aldosterone to enhance renal sodium reabsorption. Angiotensin II also has direct actions on tubular function and stimulates both proximal and distal sodium reabsorption. The proximal tubule cells contain all of the elements needed to synthesize angiotensin II locally and the peptide increases the activity of the sodium-hydrogen exchanger [72]. In the distal tubule, angiotensin II modulates this exchanger as well as the amiloride-sensitive sodium channel [69]. It is worth noting that in the context of glomerular disease and podocyte injury, the major source of increased renal angiotensin II is derived from increased filtration of liver-derived angiotensinogen rather than conversion of angiotensinogen produced within the kidney [73].

Aldosterone: The effects of aldosterone on the renal tubule include an immediate effect to increase apical membrane permeability to sodium and more extended effects that involve enhanced gene transcription and de novo synthesis of Na-K-ATPase. Aldosterone stimulates the synthesis of other enzymes involved in renal cell bioenergetics such as citrate synthase that are needed to sustain maximal tubular sodium transport [74]. Aldosterone induces a state of glucose-6-phosphate dehydrogenase deficiency in endothelial cells which may contribute to oxidant stress and altered reactivity of blood vessels in response to disturbances in sodium balance [75]. It is important to note that increased salt intake can activate the mineralocorticoid receptor via a pathway that is independent of aldosterone. In salt-sensitive animal strains, high dietary salt intake activates Rac1, a member of the Rho-guanine triphosphate hydroxylase family, which stimulates activity of the mineralocorticoid receptor. This may represent a novel pathway by which high salt intake promotes hypertension, vascular injury, and cardiovascular disease [76].

Endothelin: This vasoactive molecule is part of a family of three peptides of which endothelin-1 (ET-1) is the most important in humans [77]. It is converted in two steps from an inactive precursor to a biologically active 21-amino acid peptide. Endothelins react with two receptors, ET_A and ET_B, and cause vasoconstriction, resulting in a decrease in renal blood flow and GFR. With regard to sodium balance, the primary effect of endothelin is sodium retention mediated by the reduction in GFR. This suggests that endothelin acts in concert with angiotensin II to protect ECW compartment size under conditions of sodium deficit. However, the situation may be more complicated because direct exposure of proximal tubule and medullary collecting duct cells to endothelin in vitro inhibits sodium absorption.

Renal nerves: There is abundant sympathetic nervous innervation of the renal vasculature and all tubular segments of the nephron [78]. The efferent autonomic fibers are postganglionic and

originate in splanchnic nerves. The renal innervation is primarily adrenergic and involves α1 adrenoreceptors on blood vessels and both α1 and α2 receptors along the basolateral membrane of the proximal tubule. Renal sympathetic nervous activity is inversely proportional to dietary salt intake [78]. Renal sympathetic nervous system activity contributes to preservation of ECF volume by [1] promoting renal vasoconstriction and lowering GFR and [2] increasing sodium reabsorption. Among the catecholamines involved in adrenergic transmission, norepinephrine exerts an antinatriuretic effect. Dopamine, another sympathetic nervous system neurotransmitter, promotes a natriuresis, suggesting that there is internal regulation of the effect of nerve activation on renal sodium handling [79]. Some of the genes involved in dopamine metabolism including dopamine receptors and their regulators, G-protein-coupled receptor kinase 4 in the proximal tubule cell, may contribute to salt sensitivity in patients with hypertension and the susceptibility to CKD [80].

The sympathetic nervous system also influences sodium handling in the distal nephron. In animal models of salt-sensitive hypertension, activation of the sympathetic nervous system leads to reduced expression of WNK4 (see below). Alteration in this regulatory protein results in enhanced activity of the sodium-chloride co-transporter in the distal convoluted tubule leading to hypertension [76].

Drug-induced sodium retention and volume-dependent hypertension, e.g., with the use of cyclosporine, is mediated in part by activation of the sympathetic nervous system [81]. Increased adrenergic nervous signaling within the kidney is instrumental in the initiation of hypertension in experimental animals by causing a right shift in the pressure-natriuresis curve [79]. Alterations in WNK4 activity may be operative in calcineurin inhibitor-induced hypertension [82]. However, sodium balance is normal and ECF volume is maintained in the denervated transplanted kidney, implying that the role of the sympathetic nervous system in maintaining sodium homeostasis is redundant and can be taken over by other regulatory mechanisms [78].

Atrial natriuretic peptide (*ANP*): ANP is a 28-amino acid peptide that is a member of a group of proteins that includes C-type natriuretic peptide [83]. It is synthesized as a prohormone that is stored in granules in the cardiac atria. There are other molecular isoforms of the hormone including brain natriuretic peptide (BNP) whose circulating levels are altered and which can be monitored at diagnosis and in response to treatment in conditions such as congestive heart failure [84].

Increases in right atrial pressure provoke cleavage and release of the mature peptide. For each 1 mmHg rise in central venous pressure, there is a corresponding 10–15 pmol/L increase in circulating ANP levels. Conversely, declines in atrial pressure secondary to sodium depletion or hemorrhage inhibit ANP release. There are two receptors for ANP and both are coupled to guanylate cyclase. The activation of this enzyme results in cytosolic accumulation of cGMP, which in turn diminishes agonist-stimulated increases in intracellular calcium concentration. The principle effects of ANP are to promote an increase in GFR, diuresis, and, most importantly, natriuresis. The augmented renal sodium excretion is, in part, mediated by an increased filtered load secondary to the rise in GFR. However, ANP also exerts direct actions on renal tubular cells to diminish sodium reabsorption including inhibition the Na-K-Cl co-transporter in the loop of Henle and the amiloride-sensitive ENaC in the medullary collecting duct. Finally, ANP antagonizes the action of several antinatriuretic effectors, including sympathetic nervous system activity, angiotensin II, and endothelin. The overall effects of ANP to counteract increases in ECW compartment have been demonstrated by short-term studies in which acute infusions of ANP improved cardiac status in patients with congestive heart failure and promoted a diuresis in patients with acute renal failure [85].

Prostaglandins: The kidney contains the enzymes required for constitutive (COX-1) and inducible (COX-2) cyclooxygenase activity that convert arachidonic acid to prostaglandins [86]. The major products of these pathways are PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin (PGI_2), and

thromboxane (TXA_2). In the cortical regions, PGE_2 and PGI_2 predominate, while PGE_2 is the major prostaglandin metabolite in the medulla. These two compounds increase GFR and promote increased urinary sodium excretion. In addition, they antagonize the action of AVP. These actions may mediate the adverse effects of hypercalcemia and hypokalemia on renal tubular function [86]. The natriuretic effects of prostaglandins, in response to normal alterations in dietary sodium intake, are unclear. The role of prostaglandins as efferent signals is more apparent in conditions associated with increased vasoconstrictor tone such as congestive heart failure or reduced renal perfusion, where prostaglandins counteract the vasoconstrictor and sodium-retaining effects of high circulating levels of angiotensin II and nor-epinephrine. Inhibition of prostaglandins with cyclooxygenase inhibitors is associated with dra-matic declines in GFR and profound sodium retention and edema [87].

Prostaglandins also modulate sodium handing in the collecting tubule. Inactivation of the B1 proton pump in β-intercalated cells results in increased urinary losses of NaCl, potassium, and water leading to hypovolemia, hypokalemia, and polyuria. Inhibition of PGE2 synthesis restores activity of the ENaC and reverses the electrolyte abnormalities [88]. These novel findings under-score the importance of prostaglandins in the reg-ulation of sodium homeostasis. Moreover, they indicate that in the collecting duct, both principal and intercalated cells are instrumental in maintaining sodium balance.

Nitric oxide (*NO*): The kidney contains all three isoforms of nitric oxide synthase (NOS) – neuronal NOS in the macula densa, inducible NOS in renal tubules and mesangial cells, and endothelial NOS in the renal vasculature – involved in NO synthesis. The neuronal and endo-thelial isoforms are calcium-dependent enzymes and produce small, transient increases in NO syn-thesis. The inducible isoform is upregulated by various cytokines and inflammatory mediators, resulting in large sustained elevations in NO release.

Activation of eNOS within the kidney increases the activity of soluble guanylate cyclase and causes vasodilatation and an increase in GFR. In addition to its effect on renal blood flow and GFR, NO directly inhibits Na-K-ATPase in cul-tured proximal tubule and collecting duct cells [89, 90]. The specific isoform of NOS that is responsible for modulating urinary sodium excre-tion is not as well defined. Studies with inducible NOS, neuronal NOS, and endothelial NOS knockout mice suggest that only the first two isoforms are involved in the regulation of sodium and water reabsorption in the proximal tubule [64]. A role of NO in maintaining sodium balance under normal conditions is suggested by the observation that alterations in dietary salt intake are associated with parallel changes in urinary excretion of nitrite, the metabolic byproduct of NO [91]. In normotensive Wistar-Kyoto rats and spontaneously hypertensive rats, increased die-tary sodium intake is associated with a modest increase in urinary nitrite excretion [92]. This effect is not well documented in pediatric patients. Along with ANP and bradykinin, NO is part of the defense system against sodium excess and expan-sion of the ECW compartment. Derangements in renal NO synthesis and responsiveness to cGMP may be instrumental in the pathogenesis of salt-dependent hypertension in experimental animals [92]. There are no drugs in current use that mod-ulate sodium handling based on alteration of intrarenal NO production.

Kinins: Kinins are produced within the kidney and act via B_1 and B_2 receptors. Because the half-life of kinins in the plasma is very short, in the range of 20–40 s, it is likely that their actions in the kidney are regulated locally through produc-tion and proteolytic processing in the tissue [93]. Their principal action is to promote renal vasodilatation and natriuresis. The kinins act pri-marily in the distal tubule to reduce sodium reabsorption [93, 94].

Insulin: Insulin promotes sodium reabsorption in the proximal and distal segments of the neph-ron. It has direct effects on the Na-H antiporter in the proximal convoluted tubule [95] and on the NaCl co-transporter in the distal tubule [96]. Part of the effect of insulin may be mediated by mod-ulation of the sympathetic nervous system and WNK kinase activity [97]. The antinatriuretic

Fig. 3 Graphic illustration summarizing sensor and effector mechanisms involved in the regulation of sodium balance and ECF volume. *ANP* atrial natriuretic peptide, *NO* nitric oxide, *PG* prostaglandins
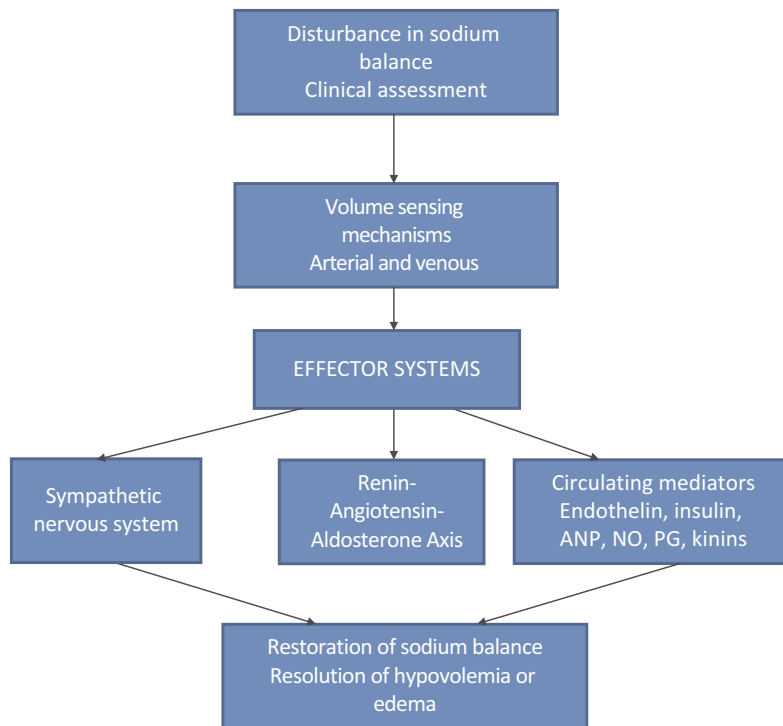
effect of insulin contributes to the hypertension observed in children with hyperinsulinemia and the metabolic syndrome. In the context of insulin and sodium, it is worth noting that a new class of drugs that have been introduced for the treatment of diabetes, namely, sodium-glucose co-transporter inhibitors, is associated with increased natriuresis and a modest reduction in blood pressure [98].

FGF23: Recent data suggest that FGF23, an important bone-derived hormone involved in phosphate homeostasis, may contribute to sodium balance [99]. It appears to act in the distal tubule to promote sodium reabsorption by the Na-Cl co-transporter via a pathway that involves the FGF23 receptor/Klotho complex, extracellular signal-regulated kinase 1/2, serum glucocorticoid-regulated kinase 1, and WNK4. This observation may account, in part, for the association of FGF23 and cardiovascular disease in children with CKD.

Adrenomedullin: Adrenomedullin is a 52-amino acid peptide that was isolated from human pheochromocytoma cells [100]. It reacts with a G-protein cell receptor and causes vasodilatation, an effect that may be mediated by increased synthesis of NO. The resultant natriuresis secondary to the increase in GFR is accompanied by direct inhibition of tubular sodium reabsorption. Its role in sodium balance is under investigation.

The WNK, with no lysine protein kinase family, are serine threonine kinases. They are responsible for the regulation of several membrane proteins in the kidney that mediate Na+ handling in the distal tubule. This family senses intracellular and extracellular ion concentrations and accordingly alters the activity of channels and transport proteins in the nephron via SPS1-related proline/alanine-rich kinase (SPAK) or oxidative stress-responsive kinase 1 (OSR1) [101]. Of particular importance are the cation-chloride co-transporters (CCCs) found throughout the tubule. The WNK family serves to help maintain appropriate blood pressure by acting on these co-transporters. WNK inhibition acts to lower blood pressure by decreasing NaCl reabsorption in the distal collecting tubule and thick ascending limb while maintaining serum K+ levels by reducing K+ secretion [101]. Figure 3 summarizes the sensor and effector mechanisms that are involved in the regulation of sodium homeostasis.

Water

AVP: The primary efferent mechanism in the maintenance of water homeostasis is AVP. This peptide fosters water retention by the kidney and stimulates thirst. The plasma AVP concentration is approximately 1–2 pg/ml under basal conditions [64, 65]. It is unknown whether there is tonic release of AVP or whether there is pulsatile secretion in response to minute fluctuations in plasma osmolality. The set point, or osmotic threshold for AVP release, ranges from 275 to 290 mosm/kg H_2O. The circulating hormone concentration rises approximately 1 pg/mL for each 1 % increase in plasma osmolality. The sensitivity of the osmoreceptors in promoting AVP release varies from person to person with some individuals capable of responding to as small as a 0.5 mosm/kg H_2O increase in osmolality and others requiring greater than a 5 mosm/kg H_2O increment to stimulate AVP release. Patients with essential hypernatremia possess osmoreceptors that have normal sensitivity but the osmotic threshold for AVP release is shifted to the right. Because the relative distribution of water between the ECW and ICW compartments is undisturbed, these patients are unaffected by their abnormally high serum sodium concentration. Although there may be sex-related differences in AVP secretion in response to abnormal water homeostasis with increased sensitivity in women, this is not a relevant clinical concern in prepubertal children.

Reliable measurement of AVP is hindered by several factors including high level (>90 %) of binding to platelets. Thus, plasma AVP measurements are influenced by the number of platelets, incomplete removal of platelets, or pre-analytical processing steps. Copeptin (CTproAVP), a 39-amino acid glycopeptide, is a C-terminal part of the precursor pre-provasopressin (pre-proAVP). Activation of the AVP system stimulates copeptin secretion into the circulation from the posterior pituitary gland in equimolar amounts with AVP. Therefore, CTproAVP directly reflects AVP concentration and it has been used clinically as a surrogate biomarker of AVP secretion [102].

*Angiotensin*: Angiotensin II serves as an efferent system in water homeostasis primarily by acting as a potent dipsogen and stimulating drinking [68]. Its role in water handling within the kidney is minor and may be related to modulation of the renal response to AVP. However, it is a potent dipsogen and stimulates thirst and drinking behavior.

Thirst: Thirst, or the consciously perceived desire to drink, is a major efferent system in water homeostasis [67]. It is estimated that for each 1 pg/mL increase in the circulating plasma AVP level, there is parallel rise of 100 mosm/kg H_2O in urinary concentration. If the basal plasma osmolality and AVP concentration are approximately 280 mosm/kg H_2O and 2 pg/mL, respectively, and the steady state urine osmolality is 200 mosm/kg H_2O, then as soon as the plasma osmolality and AVP concentration reach 290 mosm/kg H_2O and 12 pg/mL, respectively, the urine is maximally concentrated. Beyond this point, the only operational defense against a further rise in plasma osmolality is increased free water intake, underscoring the essential role of thirst as an efferent mechanism in water homeostasis. It highlights the increased risk of hyperosmolality in patients who do not have free access to water such as infants, the physically or mentally incapacitated, or the elderly [69].

Thirst is a biological function that is difficult to quantitate because it is an expression of a drive rather than an actual behavior. At present, visual analog scales using colors or faces are the most useful tools for quantitating thirst under controlled condition. There can be dissociation between water intake and the sensation of thirst as in patients with psychogenic polydipsia (e.g., schizophrenia, neurosis). It is not known whether specific drugs directly stimulate the dipsogenic response. The role of diet, e.g., high salt intake, in the regulation of thirst is also unknown. The osmotic control of thirst may be suboptimal in newborn infants and in the elderly [103].

Thirst and drinking behavior are stimulated by significant contraction of the ECF space or by hypotension. In addition, thirst and drinking behavior are modulated by signals that originate in the oropharynx and upper gastrointestinal tract. Animals with hypernatremia who are given access to water as the sole means of correcting the

Fig. 4 Graphic illustration summarizing sensor and effector mechanisms involved in the regulation of water homeostasis, osmolality, and cell volume. *AVP* arginine vasopressin
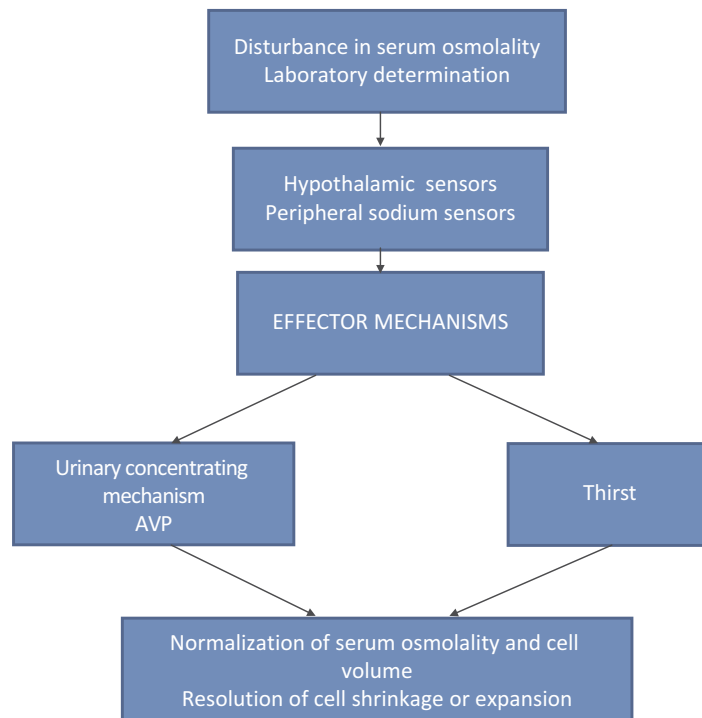
hyperosmolal state stop drinking sooner than animals corrected in part with supplemental intravenous fluid. This is most likely due to oropharyngeal stimuli that curtail drinking prior to complete normalization of plasma osmolality [104]. Figure 4 summarizes the sensor and effector mechanisms that are involved in the regulation of sodium homeostasis.

Effector Mechanisms: Sodium and Water

The kidney is the principal organ that acts in response to sensory input, delivered via neural or humoral signals, to restore ECW volume size to normal following the full range of clinical problems. Absorption of sodium across the gastrointestinal tract, modulated by chemoreceptors in the hepatic vasculature, plays a minor in body sodium homeostasis.

Sodium

GFR: In children with normal kidney function, changes in GFR are associated with parallel alterations in sodium balance. This is accomplished by glomerular-tubular balance in which load-dependent proximal tubule sodium absorption and delivery of filtrate to the distal tubule is modulated in response to GFR [105]. Changes in GFR also lead to changes in the oncotic pressure in the peritubular capillaries that influence sodium reabsorption [106]. Thus, an increased GFR is associated with higher hydrostatic pressures in the peritubular capillary network that retard fluid and solute reabsorption in the proximal tubule. Finally, tubuloglomerular feedback is activated by alterations in solute delivery to the distal nephron to bring GFR in line with alterations in tubular function. Many of the efferent signals including renin, angiotensin, NO, adenosine, and prostaglandins participate in this particular pathway. The release of these effector molecules is activated via myogenic stretch receptors and chemoreceptors located in the macula densa region of the distal nephron. Even in children with compromised renal function (GFR <30 ml/min/ 1.73 m^2), glomerulotubular balance is maintained in the face of gradual changes in GFR. However, they are unable to respond to abrupt changes in sodium balance and ECF volume changes as rapidly as healthy children and are susceptible to

volume contraction or hypervolemia if sodium intake is substantially reduced or increased over a short period of time [46].

Neural and humoral factors that lower GFR act predominantly on the vascular tone of the afferent arteriole and reduce renal blood flow and the filtration fraction. Agents in this category include adrenergic nerve stimulation and endothelin. In contrast, angiotensin II acts primarily on efferent arteriolar tone. This tends to preserve GFR more than renal blood flow and the filtration fraction (RBF/GFR) is increased. This pattern is most evident in states of compromised effective perfusion such as congestive heart failure, cirrhosis, and nephrotic syndrome [62, 63, 107]. The critical role of angiotensin II in maintaining GFR and sodium excretion in these conditions is manifest during the acute reversible functional decline in GFR that occurs after the administration of ACE inhibitors [108]. This phenomenon also explains the reduction in kidney function and sodium retention that are observed in patients with a critical renal artery stenosis in a kidney transplant following initiation of ACE inhibitor therapy [108].

Proximal tubule: Nearly 60–70 % of the filtered sodium and water load are reabsorbed in the proximal tubule. Sodium and fluid reabsorption are isosmotic in this nephron segment. These processes are driven by Na-K-ATPase activity along the basolateral membrane surface with secondary active transport of solute across the apical membrane. The bulk of sodium reabsorption is driven by the sodium-hydrogen exchanger, with a lesser contribution by other co-transport systems for glucose, phosphate, organic anions, and amino acids. The linkage between disturbances in ECF volume and sodium reabsorption in the proximal tubule is created, in part, by changes in the physical forces that govern fluid and solute movement. These include changes in peritubular capillary hydrostatic pressure, peritubular capillary protein concentration, and oncotic pressure and changes in renal interstitial pressure that modulate water and solute movement across cells (transcellular) and along the paracellular pathway.

Sympathetic nervous stimulation, norepinephrine release, and both filtered and locally synthesized angiotensin II stimulate the activity of the sodium-hydrogen antiporter and promote sodium reabsorption in conditions associated with decreased ECF volume. Conversely, ANP and the kinins act on proximal tubular cells to inhibit sodium reabsorption and limit expansion of the ECW space.

Distal nephron including collecting duct: This portion of the nephron is responsible for the reabsorption of approximately 10–25 % of the filtered sodium and water load. Under most circumstances, it adapts to changes in delivery arising from alterations in proximal tubule function. This segment of the nephron is responsive to virtually all of the humoral efferent signals and accomplishes the final renal homeostatic response to fluctuations in sodium balance. Sodium reabsorption in the distal tubule and connecting segment is responsive to circulating levels of aldosterone [74]. In the collecting tubule, mineralocorticoid-responsive sodium reabsorptive pathways in the principal cell achieve the final modulation of sodium excretion in response to alterations in sodium intake. Aldosterone enhances sodium reabsorption by inducing a number of transport proteins whose synthesis is triggered by activation of SGK1, serum, and glucocorticoid-inducible kinase [109]. The most prominent of these is the epithelial sodium channel (ENaC). This transepithelial protein is composed of three distinct chains – α, β, and γ – each of which is encoded by a separate gene [110]. The complete protein has two membrane-spanning domains with an amino and carboxyl terminus within the cell. The α-chain appears to constitute the actual sodium-conducting pathway, while the β- and γ-chains represent regulatory components that control the open/closed status of the channel. Genetic defects in each individual component have been described and linked to human disease. Thus, pseudohypoaldosteronism has been mapped to mutations in the α, β, and γ chains, and Liddle's syndrome has been attributed to truncation in the β-chain with increased ubiquitinylation and proteasomal degradation of the abnormal protein [109–111]. As noted above, recent evidence indicates that β-intercalated cells in the collecting duct also modulate sodium, potassium, and water excretion [88].

Water

AVP: AVP acts along several segments of the nephron. However, its primary site of action for maintenance of water homeostasis is the collecting tubule [112]. In that segment of the nephron, AVP reacts with the V2 receptor, a 371-amino acid protein that is coupled to a heterotrimeric G protein, along the basolateral membrane of the distal tubule and collecting duct cells. The V2 receptor gene has been localized to region 28 of the X chromosome. This epithelial cell receptor is distinct from the V1 receptor in the vasculature that is linked to Ca activation of the inositol triphosphate cascade and which mediates vasoconstrictor response to the hormone [112].

The binding of AVP to the V2 receptor activates basolateral adenylate cyclase and stimulates the formation of cAMP within the cytosol. This intracellular second messenger then interacts with the cytoskeleton, specifically microtubules and actin filaments, and promotes fusion of intramembrane particles that contain preformed water channels with the apical membrane of principal cells in the collecting duct. The AVP-induced entry of preformed water channels involves clathrin-coated pits. The withdrawal of AVP leads to endocytosis of the membrane segment containing the water channels into vesicles that are localized to the submembrane domain of the cell. This terminates the hormone signal. Recycling of water channels from vesicles to the apical membrane and then back into vesicles has been demonstrated in freeze-fracture studies of cells exposed to AVP [112]. The importance of the V2 receptor in water homeostasis is confirmed by genetic mutations and corresponding abnormalities in protein structure in children with X-linked congenital nephrogenic diabetes insipidus [113]. Conversely, activating mutations in the V2 receptor lead to increased water absorption and hyponatremia in the absence of AVP, resulting in a condition called nephrogenic syndrome of inappropriate antidiuresis [114, 115].

The water channels that mediate transmembrane movement of water across the collecting tubule in response to AVP are called aquaporins [116]. There are nine known members of this group of proteins, all of which contain six membrane-spanning domains. The first member to be identified was aquaporin-1 (originally called channel-forming integral membrane protein of 28 kD or CHIP-28), which mediates water movement across the erythrocyte membrane and along the proximal tubule. Mice that do not express AQP-1 have a normal phenotype and concentrate their urine normally. Aquaporin-2 (AQP-2) is the major AVP-sensitive water channel in the collecting tubule [117]. Immunogold electron microscopy studies have confirmed that AQP-2 represents the water channel in the cytosolic vesicles which fuse with the apical membrane following exposure of principal cells to AVP. The contribution of AQP-3 and AQP-4 to the normal urinary concentrating mechanism has been confirmed in mice that have been genetically manipulated and which do not express these two proteins [118].

The importance of AQP-2 in mediating the normal response to AVP has been verified by the discovery of mutations in the AQP-2 gene in children with non-X-linked, autosomal-recessive forms of nephrogenic diabetes insipidus [119]. Moreover, alterations in AQP-2 protein expression have been documented in other states associated with a urinary concentrating defect such as lithium exposure, urinary tract obstruction, hypokalemia, and hypercalcemia [116]. There are persistent challenges in the development of better modulators of the aquaporins including druggability of the target and the suitability of the assay methods used to identify the modulators [120].

Water reabsorption in the collecting duct is not completely dependent upon the presence of AVP. In animals that are genetically deficient in AVP (Brattleboro rats) or in patients with central diabetes insipidus, urinary osmolality increases slightly above basal levels in the face of severe ECF volume contraction. This may be the consequence of reduction in urinary flow rate along the collecting duct that enables some passive equilibration between the luminal fluid and the hypertonic medullary interstitium.

Although the collecting duct is the primary site of regulation of net water reabsorption, the

proximal tubule contributes to water balance under circumstances of decreased ECW compartment size. Whereas the proximal tubule normally reabsorbs approximately 60 % of the filtered water load, this proportion may exceed 70 % when the ECF volume is diminished. Furthermore, by decreasing fluid delivery to the distal nephron, this enhances the AVP-independent reabsorption of water along the collecting tubule. These effects may explain the clinical benefit achieved by the administration of thiazide diuretics to patients with nephrogenic diabetes insipidus [121]. The utility of hydrochlorothiazide in the management of nephrogenic diabetes insipidus also reflects increased synthesis and expression of aquaporins and sodium transporters such as ENaC and sodium-chloride co-transporter [122].

Countercurrent Mechanism

The primary locus of the urinary concentrating mechanism is the medulla and involves the thin descending limb of Henle, medullary thick ascending limb of Henle, cortical thick ascending limb of Henle, and collecting duct [123]. Sodium and water reabsorption are isosmotic in all segments of the nephron proximal to the loop of Henle. In order to concentrate or dilute the urine, water and solute must be separated to enable excretion of free water or urine that is hyperosmolal relative to plasma. This process begins in the medullary and cortical thick ascending limb of Henle where NaCl is reabsorbed independently of water, generating a hypotonic luminal fluid. This action is linked in series to the low water permeability of the distal tubule and the connecting segment, which together with continued sodium reabsorption, enhances the hypotonicity of the urine in this segment. In a secondary step, the permeability to water along this segment of the nephron is much lower than in the descending limb of the loop of Henle. This enables water to move down its osmolal gradient from the tubule lumen into the interstitium as it enters the medulla in the descending limb. Finally, the third critical component of the countercurrent mechanism is the presence of vasa recta, which perfuse the inner medulla via vascular bundles

Table 4 Factors that contribute to the countercurrent mechanism

Na-Cl-K-mediated solute absorption in the medullary thick ascending limb of Henle
Low water permeability of the distal tubule and connecting segment
High water permeability in the descending limb of Henle
Vasa recta and elimination of interstitial water volume
AVP responsiveness of the collecting tubule

that contain hairpin loop-shaped blood vessels. This facilitates efficient removal of water that exits the descending limb of Henle from the medullary interstitium without washing out the solute gradient that passively drives water reabsorption in the collecting tubule. The final effector mechanism is the alteration in the water permeability of the collecting tubule in response to AVP and generation of a concentrated urine or the excretion of solute-free water in the absence of AVP (Table 4). Conditions that disturb the normal architectural relationship between the vasculature and the tubules in the medulla such as chronic allograft nephropathy, acute interstitial nephritis, and obstructive uropathy disrupt the countercurrent mechanism and lead to a urinary concentrating defect.

Osmoprotective molecule (*compatible osmolytes*): Besides the presence of effector mechanisms to maintain water balance, cells possess a wide range of adaptive mechanisms to counteract the undesirable movement of water between the cell and the ECW during hypotonic and hypertonic states and to prevent neurological dysfunction. These include early response genes that mediate the prompt accumulation of chaperone molecules to counteract the adverse effects of altered cell size on protein function [50]. This is followed temporally by the uptake or extrusion of electrolytes as an acute response to altered size cell. Because there are inherent limits on the ability to regulate cell volume exclusively with inorganic electrolytes, the more extended response involves membrane transport and/or synthesis/degradation of a variety of compatible solutes, called osmolytes, whose cytosolic concentration can be safely altered without perturbing enzymatic activity and cell function. These

osmoprotective molecules include carbohydrates (sorbitol, myoinositol), amino acids (taurine, glutamate), and methylamines (betaine, glyceropho-sphorylcholine) [50]. They accumulate in the cytosol to preserve cell function during chronic osmolal disturbances. The cell volume regulatory response can be activated by electrolytes such as sodium or neutral molecules, e.g., urea and glucose [50]. The adequacy of the cell volume regulatory response and the accumulation of osmoprotective molecules in cerebral and renal cells depend on the rate of rise in osmolality as well as the magnitude of the absolute change [124].

Experimental data in animals and clinical experience in premenopausal women suggest that estrogens may impair the cell volume regulatory response to disturbances in plasma osmolality. This increases the risks associated with both the untreated abnormalities and therapy [125]. The cell volume regulatory adaptation is fully operational during maturation. The accumulation of osmoprotective molecules in the face of chronic hypernatremia is normal in pre-weanling rats, albeit with a higher set point to preserve the increased brain cell water content [126].

The failure to adequately account for the cell volume regulatory response to osmolal disorders contributes to some of the adverse effects associated with inappropriately rapid correction of abnormalities in plasma osmolality. Under these circumstances, there is disruption in the blood-brain barrier and activation of glial cells in the central nervous system. These lead to neurological dysfunction, specifically seizures, during the treatment of hypernatremia, osmotic demyelinating syndrome following rapid reversal of hyponatremia, dialysis disequilibrium syndrome after the initiation of dialysis in patients with AKI or CKD, and cerebral edema and brain herniation in patients with a first episode of acute diabetic ketoacidosis [127, 128].

Laboratory Assessment of Sodium and Water Balance

There are no normal values for sodium and water intake or excretion, a reflection of the wide range of normal daily dietary intake for both sodium and water. Healthy individuals are in balance and the excretion of sodium and water matches the daily intake. Therefore, laboratory assessment of sodium and water homeostasis is confined to disease states in which the clinician must determine whether renal sodium and water handling are appropriate for the clinical circumstances.

Sodium

The urine sodium concentration is not a valid index of sodium balance because the value may vary depending upon the volume and concentration of the sample. Therefore, renal handling of sodium is best evaluated using the fractional excretion of sodium (FENa). After obtaining a random urine sample and a simultaneous blood sample and measuring the sodium and creatinine concentrations in both specimens, the FENa is calculated using the following formula:

$$\begin{aligned} FENa &= \text{excreted sodium/filtered sodium} \\ &= \text{urinary sodium concentration} \times \text{urine flow rate/plasma sodium concentration} \times \text{GFR} \\ &= \frac{\text{urine sodium concentration/plasma sodium concentration}}{\text{urine creatinine concentration/plasma creatinine concentration}} \end{aligned} \tag{3}$$

This formula is based on the insertion of the creatinine clearance as a measurement of GFR in the second equation and the cancelation of the urine flow rate term in the numerator and denominator. The determination of the FENa is useful in clinical practice because it can be done using spot samples and does not require timed urine collections. In healthy individuals, the

FENa varies depending upon the daily sodium intake. However, in patients with ECF volume contraction who are responding appropriately, the FENa is less than 1 % (<3 % in neonates). Conversely, in patients with ECW compartment expansion, the FENa will exceed 3 % unless there is concomitant renal disease.

Water

The determination of the urine specific gravity or osmolality in a random sample varies depending upon the water intake in the past 2–4 h. Therefore, the assessment of water handling is best judged by determining these values under more controlled conditions such as in the water-deprived state or following administration of a water load (10–20 ml/kg body weight) to evaluate the urinary concentrating or diluting capacity, respectively.

The functional aspects of renal water handling are best assessed by determining the free water clearance. This represents the amount of solute-free water excreted by the kidney. It is calculated using the following formula:

$$
\begin{aligned}
\text{Free water clearance} &= \text{urine volume} - \text{osmolal clearance} \\
&= \text{urine volume} - [\text{urine osmolality} \times \text{urine flow rate}]/\text{plasma osmolality}
\end{aligned}
\tag{4}
$$

If the free water clearance is a positive number, then the urine/plasma osmolality ratio is less than 1, the urine is dilute, and the kidney is in a diuretic mode. When a water diuresis is maximal, the free water clearance measures the capacity of the kidney to excrete free water. Under these circumstances, urine volume is directly related to the dietary solute intake [31]. In contrast, patients who are in an antidiuretic mode have a urine/plasma osmolality ratio greater than 1 and a negative free water clearance. As the solute excretion rate increases, both the maximum values for free water clearance and free water reabsorption increase. At any given solute excretion rate, the free water clearance greatly exceeds the free water reabsorption. This indicates that the renal water homeostatic mechanisms designed to protect against overhydration and dilution of the ECW are more robust than those used to defend against water deficit and dehydration.

Overview of the Evaluation of Fluid and Water Abnormalities

In practice, the clinical information and laboratory data used to evaluate patients overlap with one another. However, in view of the different physiological roles of sodium and water balance in body fluid homeostasis, the distinct regulatory mechanisms activated to control these factors, and the varied therapeutic strategies that must be employed to restore sodium and water balance in disease states, it is essential that disturbances in sodium-waterand water balance be evaluated separately. These dual assessments are done in parallel, a reflection of the body's own method of operation.

When confronted with a child with a sodium and water disturbance, the first question is whether the size of the ECF volume is altered – is it decreased or expanded? – to the extent that perfusion of vital organs or pulmonary gas exchange is jeopardized. Depending on the severity of the problem, such patients have a life-threatening condition and may require emergency therapy such as volume resuscitation or acute dialysis.

After making this acute determination and instituting appropriate emergency therapy, it is important to grade the magnitude of the disturbance in ECF volume. There is no single or combination of laboratory tests that substitute for clinical judgment. Because acute changes in body weight always reflect alterations in sodium balance and ECW compartment size, serial measurements in body weight are the most reliable indicator of the presence and severity of

disturbances in ECF volume. However, these measurements are often unavailable or will have been done in different locations using different equipment. Therefore, the evaluation of sodium balance is based upon a wide range of clinical findings including changes in mental status, level of alertness, irritability, presence of thirst, pulse rate, blood pressure, orthostatic changes, fullness of the anterior fontanel in infants, presence of tears, dryness of the mucus membranes, skin color, elasticity of the skin or tenting, capillary refill or turgor, peripheral edema, shortness of breath, and presence of rales on auscultation of the chest. Capillary refill may be the most useful test to rapidly and accurate assess ECF volume and the response to treatment [129]. Other findings on clinical examination include urinary specific gravity and central venous pressure. Laboratory investigations include BUN, serum creatinine, and bicarbonate concentrations.

It is important to emphasize that assessment of ECF volume is a ***clinical determination***. There is no single or combination of laboratory tests that is a valid surrogate marker. Moreover, despite the frequency of clinical disturbances in sodium balance, especially ECF volume contraction, no suitable scoring has been devised to accurately and reliably distinguish different degrees of ECF volume contraction or expansion. This contrasts to the Glasgow coma score or the PRISM score that have been successfully applied to the initial assessment of patients with acute neurological or multisystem organ failure.

The third step in the evaluation of a patient with a sodium and water disturbance is to measure the plasma osmolality, which indicates an abnormal distribution of water between the ECW and ICW compartments. The most likely symptoms include confusion, irritability, lethargy, obtundation, and seizures. These manifestations overlap significantly in patients with hyperosmolality or hypoosmolality. In contrast to disorders of ECF volume, disturbances in water balance and distribution require a ***laboratory determination*** for confirmation and grading. The steps involved in the initial evaluation of a child with a disturbance in sodium and water balance are summarized in Table 5. The following

Table 5 Steps in the initial evaluation and treatment of a child with a disturbance in sodium and/or water balance

Step 1: determine if there is a life-threatening alteration in ECF volume
Volume resuscitation if there is ECF volume contraction
Consider dialysis if there is ECF volume expansion
Step 2: grade severity of defect in sodium balance
Clinical determination of ECF volume
Step 3: determine if there is a defect in water balance
Laboratory measurement of plasma osmolality

sections describe the individual clinical entities responsible for derangements in sodium and water balance and outline the general treatment of these conditions.

Sodium Balance Disturbances: Deficit and Excess

Sodium Deficit

Diagnosis and evaluation: Sodium deficits and ECF volume contraction are dangerous because decreased size of the intravascular space leads to reduced perfusion and ischemia of vital organs, namely, the brain, heart, and kidneys. In children, the absence of concomitant atherosclerosis disease or endothelial dysfunction secondary to essential hypertension, smoking, hyperlipidemia, and diabetes decreases this risk. However, there are pediatric patients who are more susceptible to the adverse consequences of hypovolemia including newborn babies in whom high circulating levels of vasoconstrictor hormones and impaired autoregulation render the glomerular microcirculation sensitive to reduced perfusion [130]. In addition, underlying diseases or medications may hinder the counter-regulatory responses to ECF volume contraction and heighten the risks of hypovolemia.

Diseases that cause sodium deficiency can originate outside the kidney or within the kidney. It is unfortunate that the word dehydration is routinely used to describe these states because it suggests that water deficit is the major pathophysiological problem. It deflects attention from the

primary defect, namely, a net negative sodium balance [131, 132]. The critical role of the ECF space and sodium balance in the pathogenesis of clinical states of volume contraction is highlighted by comparing the situation that occurs in patients with diabetes insipidus. When sodium balance is perturbed, >30 % of the fluid loss is derived from the ECW compartment provoking the rapid onset of symptoms. In contrast, only 1/12 or 8 % of the pure water loss that occurs in diabetes insipidus is derived from the ECF (1/3 X 1/4), accounting for the rare evidence of ECF volume contraction in children with central or nephrogenic diabetes insipidus (Fig. 1). The term "denatration" may provide a more accurate depiction of what is occurring in patients with primary deficits in sodium balance and contraction of the ECF volume [131].

Extrarenal causes can occur from losses of sodium in any body fluid or across any epithelial surface including the CSF, pleural fluid, biliary tree, gastrointestinal losses, or skin. They can be the result of medical treatment. CKD can cause sodium deficit because the lower GFR compromises the homeostatic capacity of the renal tubules. Alternatively, there may be primary renal sodium loss that is not the consequence of a decrease in kidney function. Finally, renal sodium reabsorption may be diminished because of reduced circulating levels or unresponsiveness to aldosterone. The major causes of sodium deficiency are summarized in Table 6.

Identifying the cause of a disturbance in sodium balance is accomplished based on a thorough history and physical examination. Previously, the degree of ECF volume contraction was categorized as mild, moderate, or severe if the changes in body weight were estimated to be <5 %, 5–10 %, or >10 %, respectively. Life-threatening ECF volume contraction was thought to represent >15 % decrease in weight. Recent data, based upon systematic body weights at the time of hospitalization and immediately after correction of the sodium deficit, suggest that these numbers overestimate the degree of sodium deficit and that the ECF volume contraction is better estimated to be <3 %, 3–6 %, and >6 % with >9 % change in body weight representing an emergency [133].

Table 6 Causes of net sodium deficit

Renal causes
Compromised GFR
Acute decrease in sodium intake or increased losses
Tubular disorders
Osmotic diuresis
Diabetic ketoacidosis
Renal tubular acidosis
Renal Fanconi syndrome
Pseudohypoaldosteronism
Obstructive uropathy
Bartter's syndrome
Renal dysplasia/hypoplasia
Central nervous system
Cerebral salt wasting
CSF drainage procedures
Hepatobiliary system
Biliary tract drainage
Gastrointestinal tract
Infectious diarrhea
Chloride diarrhea
Laxative abuse
Malignancy (carcinoid, tumor related)
Adrenal diseases
Salt-losing congenital adrenal hyperplasia
Addison's disease
Skin losses
Cystic fibrosis
Neuroectodermal diseases
Burns

If the losses are extrarenal, then renal sodium reabsorptive mechanisms will be activated and the urinary specific gravity will be >1.015 and the FENa will be low, generally <1 % except in infants. The failure to increase the urine concentration and lower FENa in the face of clinical signs of ECF volume contraction points toward a renal or adrenal cause for the disorder. A renal ultrasound documenting the presence of small, misshaped kidneys or hydronephrosis may be indicative of congenital abnormalities of the kidney such as dysplasia or obstructive uropathy. Adrenal insufficiency is suggested by concomitant hyponatremia and hyperkalemia.

Treatment: If the ECW compartment size is so severely contracted that vital organ perfusion is compromised, based upon an altered mental

status, orthostatic changes, and azotemia, then fluid resuscitation must be initiated on an emergent basis. This is necessary to prevent the development of AKI, which may occur if there is sustained hypotension and renal ischemia secondary to ECF volume contraction. The risk of AKI is higher in children with preexisting renal disease, who are receiving nephrotoxic medications or who have hemoglobinuria or myoglobinuria, e.g., crush injury or compartment syndrome. If there is no evidence of cardiac or pulmonary disease, then the optimal therapy under these conditions is infusion of isotonic crystalloid (0.9 % NaCl, Ringer's lactate), 20 ml/kg body weight. This fluid is appropriate regardless of the initial serum sodium or osmolality. Concerns about infusing Ringer's lactate are misplaced in view of the low potassium concentration (4 mmol/L) in this solution. Transfusion of whole blood is optimal for treatment of hemorrhagic shock. However, in all other circumstances, infusion of crystalloid solutions avoids difficulties caused by extravasation of the colloid into the interstitial compartment. A systematic review of the literature does not support the use of colloid solutions for volume replacement in critically ill patients [134]. Thus, in general, there is no proven benefit of providing colloid versus crystalloid solutions for the initial treatment of shock and organ hypoperfusion [135]. In addition, a meta-analysis has demonstrated that the use of synthetic colloids such as hydroxyethyl starch is associated with a higher risk of AKI and the need for implementation of renal replacement therapy compared to any other alternative fluid [136]. The infusion should be as rapid as possible and the fluid dose should be repeated as often as necessary to achieve some evidence of clinical improvement such as improved mental status, decrease in pulse, rise in blood pressure, or improved capillary refill. A catheter should be placed in the bladder to facilitate monitoring of urine output, especially in patients with preexisting renal or cardiopulmonary disease who may be more sensitive to sudden changes in ECF volume.

After correcting life-threatening hypoperfusion, a fluid repletion plan should be initiated as soon as possible. Preference should be given to correcting sodium and electrolyte deficits with oral rehydration solutions (ORS). In general, patients can be repleted with a rapid (1–2 h) intravenous infusion to restore ECF volume followed immediately by initiation of ORS [137]. The only conditions that represent contraindications to the use of ORS are impaired neurological status, persistent vomiting, or diseases associated with mucosal damage in the gastrointestinal lumen.

ORS fluids introduced by the World Health Organization contain sodium 90, potassium 20, bicarbonate 30, chloride, and glucose 111 mmol/L (20 g/L). The sodium and glucose are present in a molar ratio that maximizes the secondary active uptake of these solutes via the sodium-glucose co-transporter across the gastrointestinal epithelium. These transporters retain activity in the context of secretory diarrhea and only become impaired when there is extensive mucosal damage. Water is absorbed passively down its osmolal gradient. The presence of other solutes such as potassium and bicarbonate are not critical to the successful utilization of ORS. These fluids have been utilized for over 30 years. They can be administered ad libitum in response to the child's own thirst and they are effective and safe with minimal occurrence of hypernatremia or hyperkalemia. Various alternatives to glucose such as rice-syrup or amylase-resistant starch may facilitate sodium and water reabsorption from ORS, decrease fecal fluid loss, and shorten recovery time after an episode of cholera [138, 139]. Clinical studies are needed to confirm the utility of these additives because they may increase the cost and decrease the shelf life of ORS. These are important considerations in developing countries where there is a high incidence of infectious diarrhea in infants and children.

When parenteral therapy is required to correct sodium and water deficits, the following guidelines can be applied when devising a therapeutic plan. First, in the absence of reliable data regarding the acute weight loss, it is easiest to calculate maintenance and deficit therapy based on the current weight and the clinical estimate of the percentage decrease in body weight. Second, it is

advisable to discount any emergency fluid therapy, such as bolus infusions of isotonic saline, in computing the total corrective fluid prescription. Third, if the clinical problem has developed in less than 48 h, then it should be considered an acute process and the sodium and fluid losses are derived from the ICW and ECW in the ratio of 80–20 %. If the patient has been ill for more than 48 h and the process is chronic, then the sodium and fluid losses are derived from the ICW and ECW in the ratio of 60–40 %. Under most conditions in which the sodium and water losses are isotonic, the ECW portion of the loss, in liters, can be multiplied by 140 mmol/L to determine the absolute sodium loss. Similarly, the ICW portion of the loss, in liters, can be multiplied by 140 mmol/L to determine the absolute potassium deficit. If the ECW and ICW fluid losses together with the respective sodium and potassium deficits are added to the maintenance requirements, then a total fluid volume can be determined. After selecting a fluid that most closely approximates the total sodium and water losses, the total fluid volume is divided by the time frame of the correction to determine the intravenous infusion rate. It is important to monitor the child and replace ongoing losses to insure that there is full resolution of the underlying clinical problem.

Example: If a 10 kg child is judged to have a 5 % decrease in body weight over 36 h, then the total fluid deficit of 500 ml can be divided into two components – 400 ml ICW with 56 mmol potassium and 100 ml ECW containing 14 mmol sodium. The daily maintenance water and sodium requirements are 1,000 ml and 30 mmol sodium. Adding these two quantities together results in a fluid that closely resembles 0.25 % saline (37 mmol NaCl/L) containing 30 mmol KCl/L and the infusion rate is approximately 60 ml/h if the correction is designed to occur over 24 h.

Sodium Excess

Diagnosis and evaluation: These conditions, which generally are less common than sodium deficit, are evidenced by clinical signs of ECF volume expansion. They can arise secondary to exogenous addition of sodium or abnormal retention of endogenous sodium. Because the normal kidney has the adaptive capacity to rapidly excrete a sodium load, in order for the excess sodium to cause clinical symptoms and signs, there must be a concomitant factor that limits natriuresis.

Common causes of excess exogenous sodium are salt-water drowning, ingestion of a diet abnormally high in sodium, or therapeutic infusion of sodium-containing intravenous solutions, such as sodium bicarbonate during the resuscitation after a cardiopulmonary arrest. Examples of dietary excess of sodium include errors in the preparation of infant formulas. The widespread use of premixed baby formulas may decrease the incidence of these accidents.

Conditions associated with excessive endogenous sodium retention include AKI and the edema states, namely, nephrotic syndrome, cirrhosis, congestive heart failure, and gastrointestinal disease (malabsorption or protein-losing enteropathy). In the first condition, which may occur due to glomerulonephritis or acute tubular necrosis, the sodium retention is directly related to the decrease in GFR and diminished filtration of sodium. In the later four states, renal sodium and water reabsorption are activated by a combination of mechanisms that are termed, underfill and overfill. A critical review of the evidence in patients with nephrotic syndrome suggests that those diseases that are associated with an inflammatory infiltrate in the kidney develop primary sodium retention and overfilling of the ECF volume. This histopathological feature is absent in minimal change nephrotic syndrome and the underfill mechanism predominates [140]. Thus, in nephrotic syndrome, total body sodium excess may be coupled with a diminished, normal, or expanded effective ECF volume. This explains the normal distribution of PRA values and wide range of measured plasma volume in these patients. The causes of net total body sodium excess are summarized in Table 7.

The major clinical problems that accompany these conditions are related to pulmonary venous congestion, impaired gas exchange, and dyspnea. In idiopathic nephrotic syndrome, the intra-alveolar pressure is often sufficient to prevent

Table 7 Causes of net sodium excess

Exogenous sodium
Salt-water drowning
Errors in formula preparation
Infusion of hypertonic sodium solutions
For example, after cardiopulmonary arrest
Endogenous sodium
Acute renal failure (glomerulonephritis, ATN)
Nephrotic syndrome
Cirrhosis
Congestive heart failure

frank pulmonary edema. However, in other circumstances, intrinsic capillary leak together with lowered plasma oncotic pressure promotes the development of pulmonary interstitial fluid. Peripheral edema may be associated with skin infection, peritonitis, or thromboembolic events.

Conditions associated with sodium excess should be evident on physical examination. The FENa will be high if there is sodium loading and renal function is normal. In contrast, in the states characterized by retention of endogenous sodium, the FENa will be very low. The FENa is more useful than the urinary specific gravity because the later is likely to be elevated in all cases of sodium excess.

Therapy: The optimal therapy is targeted at correcting the underlying disease. This is most important in patients with cirrhosis, congestive heart failure, or gastrointestinal disease. Ancillary therapies include administration of diuretics to facilitate urinary sodium excretion. Although thiazide diuretics may be adequate, more potent loop diuretic may be required if the GFR is diminished. Potassium-sparing diuretic such as amiloride or spironolactone may be added to attenuate diuretic-induced hypokalemia. Patients with nephrotic syndrome may require combinations of diuretic agents that act in the proximal (e.g., metolazone) and distal (e.g., furosemide) segments of the nephron to promote an adequate natriuresis and diuresis. Infusions of albumin (1 g/kg body weight) can augment the medication-induced diuresis, especially in those with severe ECF volume contraction, reduced GFR, and azotemia [141]. In the most severe

cases, acute dialysis using peritoneal or hemodialysis techniques may be necessary to foster rapid clearance of excess sodium. Finally, continuous hemofiltration may be a safe and effective means to rapidly remove sodium and water in severely ECF-overloaded children with nephrotic syndrome [142].

Water Balance Disturbances: Deficit and Excess

Hyponatremia

Diagnosis and evaluation: Patients with hyponatremia have relative or absolute expansion of the ICW compartment. If renal function is normal, the excess free water is rapidly eliminated within 2–4 h. Therefore, for hyponatremia to occur, there must be continued AVP release that is inappropriate to the serum sodium concentration and the patient must have continued access to free water. The symptoms and signs of hyponatremia, which generally involve central nervous system dysfunction, are vague and nonspecific. Laboratory confirmation is required to diagnose this abnormality. The presence of hyponatremia is not informative about the status of the ECF volume, and this later issue must be assessed clinically to determine whether the child has hypovolemic hypotonicity, isovolemic hypotonicity, or hypervolemic hypotonicity.

Hyponatremia is not uncommon in newborns, especially in preterm very low-birth-weight infants. Most often, hyponatremia is a result of impaired water excretion caused by excessive arginine vasopressin (AVP). It can also be caused by the immaturity of the renal tubular sodium reabsorption mechanisms, which result in excessive urinary sodium loss [143]. Hyponatremia is dangerous in newborns because sodium is a permissive growth factor and chronic deficiency is associated with impaired muscle, skeletal, and neural tissue growth and development [144]. Hyponatremia has also been linked to cerebral palsy, sensorineural hearing impairment, and intracranial hemorrhages. When the hyponatremia

is severe, less than 120 mEq/L, there is a risk of hyponatremic encephalopathy and possibly death [143, 145]. As such, it is important to recognize hyponatremia in infants early and institute the appropriate treatment to ensure proper growth and neurocognitive development.

In older children, hyponatremia represents one of the common electrolyte disorders in hospitalized patients. The incidence ranges from 12 % in patients with intracranial tumors who undergo neurosurgical procedures [146] to 38 % in patients with cirrhosis and refractory ascites [147]. In all clinical circumstances hyponatremia is an indicator of a heightened risk for adverse neurological outcomes and mortality.

All biochemical analyzers currently in use at large medical centers assay sodium concentration in the aqueous phase of serum and yield an accurate determination of the sodium level. Therefore, the entity called pseudohyponatremia is no longer clinically relevant. In contrast, the reduced serum sodium concentration noted in patients with increased circulating levels of an impermeant solute such as mannitol, urea, contrast media, or glucose in patients with diabetic ketoacidosis is genuine and reflects osmotic redistribution of water from the ICW to the ECW space. The phenomenon is reflected in the following formula which enables adjustment of the serum sodium in patients with severe hyperglycemia:

$$
\text{"Physiological" sodium concentration} = \text{measured serum sodium concentration} + 1.6 \times [\text{each } 100\,\text{mg/dl increment in serum glucose above } 100\,\text{mg/dl}] \tag{5}
$$

The most common clinical causes of hyponatremia are classified by the concomitant ECF volume status in Table 8. In some diseases, such as congestive heart failure, the degree of hyponatremia reflects circulating AVP levels and sympathetic nervous system activation and provides a marker of disease severity. A relationship between the degree of hyponatremia and the clinical disturbance has not been demonstrated in patients with nephrotic syndrome or cirrhosis.

The syndrome of inappropriate AVP or ADH (SIADH) release causes hyponatremia with mild to modest ECF volume expansion. It can occur as a consequence of central neurological lesions, pulmonary disease, or tumors. In addition, drugs can result in abnormal secretion or action of AVP and lead to chronic hyponatremia. A list of these agents is provided in Table 9. The diagnosis of SIADH requires confirmation that the urine is excessively concentrated relative to the plasma osmolality without evidence of ECF volume contraction or adrenal or thyroid insufficiency. These two hormones are required to maintain the low water permeability of the collecting duct in the absence of AVP. Deficiencies of either hormone impair free water clearance leading to euvolemic

hyponatremia. In practice, diagnosing SIADH requires comparison of the urine specific gravity or osmolality with the concurrent serum osmolality. The urine should normally be maximally dilute if the serum sodium concentration is <130 mmol/L or the plasma osmolality <270 mosm/kg H_2O. A urinary sodium concentration >40 mmol/L is an adequate evidence against ECF volume contraction.

Treatment: In all cases, the first line of therapy should be directed at the underlying cause of the low serum sodium concentration. However, hyponatremia often warrants specific corrective treatment. Much ink has been spilled in detailing the appropriate therapy of this electrolyte abnormality. At times, this issue has been quite contentious and the world has been divided into two supposedly distinct camps – those who advocate "rapid" versus "slow" correction of hyponatremia. The former group asserts that hyponatremia has direct adverse effects on central nervous system function including impaired oxygenation that can lead to seizures or cardiopulmonary collapse prior to initiation of therapy [148]. Such a sequence of events has been documented in experimental animals with acute

Table 8 Causes of hyponatremia

Hypovolemic: ECF volume contraction
Renal
Mineralocorticoid deficiency
Mineralocorticoid resistance
Diuretics
Polyuric acute renal failure
Salt-wasting renal disease
Renal Fanconi syndrome
Renal tubular acidosis
Metabolic alkalosis
Bartter's syndrome/Gitelman's syndrome
Gastrointestinal
Diarrheal dehydration
Gastrointestinal suction
Intestinal fistula
Laxative abuse
Transcutaneous
Cystic fibrosis
Heat exhaustion
"Third-space" loss with inadequate fluid replacement
Burns
Major surgery, trauma
Septic shock
Euvolemic: normal ECF volume
Glucocorticoid deficiency
Hypothyroidism
Mild hypervolemia: ECF volume expansion
Reduced renal water excretion
Antidiuretic drugs
Inappropriate secretion of ADH
Hypervolemic: ECF volume expansion
Acute renal failure (glomerulonephritis, ATN)
Chronic renal failure
Nephrotic syndrome
Cirrhosis
Congestive heart failure
Psychogenic polydipsia/compulsive drinking

Table 9 Drugs that cause water retention and the syndrome of inappropriate AVP release according to mode of action

Increasing water permeability of the nephron
AVP (arginine or lysine vasopressin)
Vasopressin analogs, e.g., 1-deamino, 8-D-arginine vasopressin (DDAVP)
Oxytocin
Promoting AVP release
Barbiturates
Carbamazepine
Clofibrate
Colchicine
Isoproterenol
Nicotine
Vincristine
Inhibition of prostaglandin synthesis
Salicylates
Indomethacin
Acetaminophen (paracetamol)
Other nonsteroidal anti-inflammatory drugs
Potentiation of the action of AVP
Chlorpropamide
Cyclophosphamide

hyponatremia [149]. This risk may be especially prominent in premenopausal women. In contrast, there are others who emphasize the cerebral cell volume regulatory response to hyponatremia and highlight the risk of brain cell dehydration and osmotic demyelinating syndrome in patients who are corrected too quickly [150].

Taking into account the entire literature on the subject, current evidence suggests that the risk of hyponatremia is more closely related to the acuity of the change rather than the absolute size of the drop in serum sodium concentration [151]. Thus, therapy should be guided by the time frame in which hyponatremia has developed. If the hyponatremia is acute, i.e., <12 h in duration, then the brain will behave as a perfect osmometer leading to potentially life-threatening cerebral cell swelling. Under these circumstances, there is an urgent need to rapidly reverse the hyponatremia to counteract cell swelling. Clinical experience indicates that infusion of a 3 % NaCl solution (513 mmol/L) in a volume designed to raise the sodium concentration by 3–5 mmol/L is sufficient to halt central nervous system dysfunction [152]. The benefits and lack of adverse effects of acute correction have been confirmed in a series of 34 infants and children with acute water intoxication caused by the ingestion of dilute infant formula [153]. After this is achieved, the hyponatremia can be corrected more slowly. There is preclinical evidence that administration

of urea but not steroids can attenuate the adverse neurological consequences of rapid correction of hyponatremia with hypertonic saline or a vasopressin antagonist [154]. This requires confirmation in children with hyponatremia.

Example: If a 6-year-old child weighing 20 kg develops a seizure after a tonsillectomy and is noted to have a serum sodium concentration of 115 mmol/L, then 36–60 mmol of sodium are needed to raise the sodium concentration by 3–5 mmol/L. This is accomplished by infusing 72–120 ml of the hypertonic saline infusion.

If hyponatremia has developed over more than 12 h or if the duration of the problem is unclear, especially in the absence of signs of neurological dysfunction, then slow correction is the prudent course of action [150, 151]. The current definition of slow correction includes two features: (1) the rate of rise in serum sodium concentration should be <0.6 mmol/L throughout the correction phase and (2) the total increment and/or the final serum sodium concentration after 48 h of treatment should not exceed 25 mmol/L or 130 mmol/L, respectively. The more cautious criterion should be applied depending on the initial serum sodium level. If a child develops acute changes in mental status or new neurological findings, during or shortly after the fluid treatment, then a serum sodium concentration should be checked. Imaging studies, specifically an MRI of the brain, may reveal the changes of osmotic demyelinating syndrome.

There are several therapeutic options for patients with SIADH whose underlying cause cannot be corrected. Restriction of free water intake to match insensible losses and urine output may be adequate to stabilize the serum sodium concentration. If this is not well tolerated, then the administration of furosemide 1–2 mg/kg per day to promote a hypotonic diuresis together with oral administration of NaCl 1–2 g per day may correct the hyponatremia. If these measures fail, consideration can be given to treatment with lithium or demeclocycline, two drugs that interfere with AVP action in the collecting tubule to foster excretion of free water and raise the serum sodium concentration [155].

Finally, non-peptide vasopressin receptor antagonists, the vaptans that bind to the V2 receptor in the collecting duct and block AVP action, have been developed to treat chronic hyponatremia [156, 157]. This results in diuresis without electrolyte loss, termed aquaresis, reducing total body water and raising the serum concentration of sodium, thus correcting hyponatremia.

Vaptans have been approved for use in the treatment of hypervolemic or euvolemic hyponatremia in adults. They are not indicated in patients with hypovolemic hyponatremia. Vaptans have proven useful in the treatment of congestive heart failure and chronic liver failure, both of which are frequently associated with hypervolemic hyponatremia, and SIADH when associated with euvolemic hyponatremia. Conivaptan was the first FDA-approved agent in this class and is useful for short-term intravenous use. Tolvaptan is an oral agent that has been demonstrated to safely correct hyponatremia in several dose-response studies involving adults with euvolemic hyponatremia or hypervolemic hyponatremia [158]. Safety and efficacy of these drugs have not been assessed in pediatric patients. Randomized control trials of the use of vaptans in children with euvolemic hyponatremia are underway. The results may demonstrate that vaptans have an important role in treating newborns and children with hyponatremia due to excessive AVP.

Hypernatremia

Diagnosis and evaluation: Hypernatremia may arise due to excessive intake of sodium and ECF volume expansion. However, excessive water loss relative to the sodium deficit with hypovolemia is far more common. In a recent survey of hypernatremia in hospitalized children, the vast majority had significant underlying medical problems and 76 % of the cases were secondary to inadequate water intake [159]. The prevalence of this electrolyte abnormality is much lower than hyponatremia. One of the common causes is diarrheal illness in infants; however, the reduction in

the sodium concentration of most baby formulas to match the level in human breast milk has resulted in a dramatic decrease in the incidence of hypernatremic dehydration. Nonetheless, changes in medical practice with early discharge of newborn infants after delivery have resulted in the steady occurrence of hypernatremic dehydration in breastfed babies [160]. Patients with hypernatremia have relative or absolute contraction of the ICW compartment. Similar to the situation with hyponatremia, the clinical clues to the presence of hypernatremia are nonspecific and laboratory confirmation is mandatory to diagnose this abnormality. Moreover, like hyponatremia, hypernatremia must be evaluated in light of the clinically determined ECF volume status.

Patients with hypernatremia and ECF volume expansion are easy to diagnose. The children who represent a serious problem are those with hypovolemia. They may have some distinct features including a marked irritability, a high-pitched cry, and a doughy skin texture. Because the hyperosmolality of the ECW compartment provokes movement of water from the ICW down its osmolal gradient, these patients preserve ECF volume until late in the disease course. Their illness is usually chronic and there is a greater contribution of the ICW to the water and electrolyte deficits. Assessment of the FENa is useful in assessing the ECF volume in these patients. The causes of hypernatremia are listed in Table 10.

Treatment: Because children with hypovolemic hypernatremia are usually very ill, they often require bolus infusions of isotonic saline to restore organ perfusion. Once this is accomplished, then the fluid regimen should include the maintenance fluids, the estimated deficit with the assumption that 60 % is derived from the ECW and 40 % from the ICW. In addition, there is a free water deficit. This can be calculated from the following formula:

$$\text{Water deficit(in ml)} = 0.6 \times \text{body weight} \times [\text{actual serum sodium concentration}/140 - 1] \quad (6)$$

This formula may overestimate the water deficit and it has been recommended that the following alternative equation be used to estimate the increase in serum sodium concentration that will be achieved following the infusion of 1 l of a given solution [161]:

$$\text{Change in sodium concentration} = [\text{infusate Na}^+ - \text{serum Na}^+]/\text{total body water} + 1 \quad (7)$$

Finally, with regard to the rate of correction, the standard practice is to correct hypovolemic hypernatremia gradually over at least 48 h. After the groundbreaking work of Finberg et al. [162], the risk of cerebral edema following rapid correction of chronic hypernatremia is now attributed to the inability of brain cells to extrude the osmoprotective solutes that accumulate during sustained hyperosmolal conditions in parallel with the decline in plasma osmolality during fluid therapy [163, 164]. Therefore, the osmolal gradient will be reversed with plasma osmolality lower than cerebral cell osmolality leading to ICW expansion and clinical signs of cerebral edema, findings that have been confirmed in NMR spectroscopy studies of the brain [164]. The experimental observations were confirmed in a randomized trial, which demonstrated that the safest and most effective fluid therapy for hypovolemic hypernatremia is 0.18 % NaCl given slowly over 48 h compared to 0.45 % saline given slowly or rapidly over the same time period [165]. Because hyperosmolality impairs insulin and PTH release, patients should be monitored for hyperglycemia and hypocalcemia during the correction period.

Table 10 Causes of hypernatremia

Hypovolemic: ECF volume contraction
Gastrointestinal (diarrhea and vomiting)
Evaporative (high fever, high ambient temperature)
Hypothalamic diabetes insipidus (ADH deficiency)
Head trauma
Infarction (Sheehan's syndrome)
Tumors (e.g., craniopharyngioma)
Histiocytosis
Degenerative brain diseases
Infections
Hereditary central diabetes insipidus (usually dominant)
Idiopathic
Nephrogenic diabetes insipidus (ADH resistance)
Chronic renal failure
Hypokalemia
Hypercalcemia
Damage to renal medulla
Sickle cell disease
Nephronophthisis
Renal papillary necrosis
Chronic pyelonephritis (reflux nephropathy)
Euvolemic: normal ECF volume
Unconscious patients
Infants
Lack of access to water (lost in the desert)
Primary adipsia
Essential hypernatremia (osmoreceptor destruction or malfunction)
Hypervolemic: ECF volume expansion
Inappropriate IV fluid therapy
Salt poisoning
Mineralocorticoid excess

References

1. Thomas DR, Cote TR, Lawhorne L, Levenson SA, Rubenmstein LZ, Smith DA, Stefanacci RG, Tangalos EG, Morley JE. Understanding clinical dehydration and its treatment. J Am Med Dir Assoc. 2008;9:292–301.
2. Fatehi P. Salt and water: a brief natural history. Kidney Int. 2008;64:3–4.
3. Shaffer SG, Bradt SK, Hall RT. Postnatal changes in total body water and extracellular volume in the preterm infant with respiratory distress syndrome. J Pediatr. 1986;109:509–14.
4. Skorecki KL, Brenner BM. Body fluid homeostasis in man. Am J Med. 1981;70:77–88.
5. Holliday MA. Extracellular fluid and its proteins: dehydration, shock, and recovery. Pediatr Nephrol. 1999;13:989–95.
6. Nielsen S, Kwon TH, Frokiaer J, Agre P. Regulation and dysregulation of aquaporins in water balance disorders. J Intern Med. 2007;261:53–64.
7. Devuyst O. Water transport across biological membranes: Overton, water channels, and peritoneal dialysis. Bull Mem Acad R Med Belg. 2010;165:250–5.
8. Kaplan JH. Biochemistry of Na,K-ATPase. Annu Rev Biochem. 2002;71:511–35.
9. Huang CL, Kuo E. Mechanism of disease: WNK-ing at the mechanism of salt-sensitive hypertension. Nat Clin Pract Nephrol. 2007;3:623–30.
10. Trachtman H, Futterweit S, Tonidandel W, Gullans SR. The role of organic osmolytes in the cerebral cell volume regulatory response to acute and chronic renal failure. J Am Soc Nephrol. 1993;12:1913–9.
11. Kopp C, Linz P, Dahlmann A, et al. 23Na magnetic resonance imaging determined tissue sodium in healthy subjects and hypertensive patients. Hypertension. 2013;61:635–40.
12. Titze J, Dahlmann A, Lerchl K, Kopp C, Rakova N, Schroder A, Luft FC. Spooky sodium balance. Kidney Int. 2014;85(4):759–67.
13. Dahlmann A, Dorfelt K, Eicher F, Linz P, et al. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. Kidney Int 2015;87:434–41.
14. Glaser DS. Utility of the serum osmolal gap in the diagnosis of methanol or ethylene glycol ingestion. Ann Emerg Med. 1996;27:343–6.
15. Schelling JR, Howard RL, Winter SD, et al. Increased osmolal gap in alcoholic ketoacidosis and lactic acidosis. Ann Intern Med. 1990;113:580–2.
16. Lava SAG, Biachetti MG, Simonetti GD. Sodium intake in children and its consequence on blood pressure. Pediatr Nephrol. 2014; online.
17. Haycock GB. The influence of sodium on growth in infancy. Pediatr Nephrol. 1993;7(6):871–5.
18. Wassner SJ. Altered growth and protein turnover in rats fed sodium-deficient diets. Pediatr Res. 1989;26:608–13.
19. Reungjui S, Hu H, Mu W, Roncal CA, Croker BP, Patel JM, Nakagawa T, Srinivas T, Byer T, Simoni J, Sitprija V, Johnson RJ. Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. Kidney Int. 2007;72:1483–92.
20. Wassner SJ. The effect of sodium repletion on growth and protein turnover in sodium-depleted rats. Pediatr Nephrol. 1991;5:501–4.
21. Al-Dahhan J, Jannoun L, Haycock G. Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age.

indicative of renal salt wasting, either from an intrinsic tubulopathy or from early diuretic effect. Less commonly, adrenal insufficiency can cause sodium wasting from the cells of the distal nephron. Such a deficiency can arise from an intrinsic endocrine defect such as congenital adrenal hyperplasia related to 21-hydroxylase deficiency, from some secondary impairment of adrenal function caused by infection, bleeding, or malignancy or from pharmacologic adrenal suppression without adequate replacement therapy. In the setting of adrenal insufficiency, provision of appropriate adrenal hormone replacement as well as adequate sodium and water proves therapeutic. With renal salt wasting, supplementation with sodium and any other electrolytes exhibiting impaired renal reabsorption is useful.

Hyponatremia: Normal or Expanded Volume and Urine Na $<$ 20 mEq/L

Normal or increased circulating volume and random urine sodium excretion <20 mEq/L can be seen in conditions where there is an excess of both total body water and total body sodium. The three major disorders that cause this type of hyponatremia are the nephrotic syndrome, hepatic failure related to cirrhosis, and cardiac failure. In all these conditions, there is a state of sodium and water avidity related to high levels of ADH and aldosterone. Most commonly, this is in the setting of preexisting total body sodium overload as evidenced by edema. In all of these conditions, despite the increased extracellular or circulating volume, the effective circulating volume is often depressed. As a result of this ineffective perfusion of the tissues, sodium and water avidity is only heightened by stimulation of the renin–aldosterone–angiotensin axis, further exacerbating the total body excess of salt and water. Appropriate therapy includes striking a balance between interventions promoting the maintenance of effective circulating volume and restricting the provision of excess water and sodium which will only contribute to further total body water and sodium overload.

Hyponatremia: Normal or Expanded Volume and Urine Na $>$ 20 mEq/L

Hyponatremia in the setting of normal or increased effective circulating volume is always related to persistent ADH effect [15]. If the random urine sodium value is >20 mEq/L, the most common clinical scenario is the syndrome of inappropriate antidiuretic hormone secretion or SIADH. SIADH can arise from disparate clinical conditions including the postoperative child, the child with significant pain, or the child with pulmonary disease. Ill children may be at risk for both inappropriate ADH secretion and inappropriate ADH effect [74]. In SIADH, despite a state of hypoosmolality, the urine is inappropriately concentrated as a result of ongoing ADH secretion and ADH-mediated water reabsorption from the distal nephron. Appropriate therapy for SIADH includes restricting water intake and attending to any underlying clinical factors predisposing to this syndrome. Provision of fluids containing higher concentrations of sodium will not necessarily increase serum sodium without attention to concomitant water restriction.

Normal or increased extracellular volume and high urine sodium concentration can also be seen in the setting of renal failure as both glomerular filtration and water clearance falls, while the fractional excretion of sodium rises. A more unusual cause of this form of hyponatremia is polydipsia, usually psychogenic in nature. Such water intoxication is rare in children but can occasionally be seen with emotional or psychiatric illness in older children or with infants inappropriately provided with large volumes of water or very hypotonic fluid in a repetitive fashion by a caretaker. In both these circumstances, restriction of the volume of free water ingested on a daily basis may be beneficial.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration greater than 150 mEq/L. Generally, even higher serum sodium values can be tolerated with the most significant clinical effects not

occurring until levels exceed 160 mEq/L. As with hyponatremia, hypernatremia is more commonly a reflection of a problem with water homeostasis than sodium balance [75]. In most instances, the patient has a relative deficiency of water for normal extracellular solute content.

Since sodium is the major determinant of plasma osmolality, as serum sodium levels rise, serum osmolality concomitantly increases. Increases in serum osmolality are sensed by hypothalamic osmoreceptors, triggering ADH release from the posterior pituitary as serum osmolality increases over 280 mOsm [76]. In the setting of high ADH, there can then be increased reabsorption of free water from filtrate in the cortical collecting duct. Increased serum osmolality also causes a sensation of thirst and triggers increased fluid intake. All of these mechanisms serve to re-equilibrate serum osmolality and sodium levels before clinically significant hyperosmolality or hypernatremia occurs.

Outside infancy, hypernatremia as a result of sodium excess or salt poisoning is infrequent. Its major cause is improper preparation of powdered or liquid concentrated formula resulting in a hypertonic, hypernatremic solution. Since infants do not have free access to water, they cannot respond to their increasing sense of thirst as they develop such hypernatremia. As caregivers continue to provide the same incorrectly prepared formula for further feedings, there is further salt loading. In addition, young infants are unable to excrete sodium loads as efficiently as older children and this limits the intrinsic renal response. Iatrogenic sodium loading can also be seen in children who receive large doses of sodium bicarbonate during resuscitation, because of persistent acidosis, or in children who have been given inappropriate amounts of sodium in peripheral nutrition. Iatrogenic sodium loading can also be seen in the child receiving repeated large volumes of blood products since these are generally isotonic or sodium-rich solutions.

Children who have hypernatremia from sodium excess should exhibit the physical signs and symptoms of an expanded extracellular space. They frequently have peripheral edema and may have hypertension or symptoms of pulmonary edema. These children can respond to therapy aimed at augmenting sodium elimination. The use of diuretics and the provision of adequate free water decrease the total body sodium burden. Rarely, dialysis may be necessary when the hypernatremia must be corrected rapidly [77, 78].

Hypernatremia as a result of salt loading is rare and the pediatric clinician is much more likely to see hypernatremia stemming from a free water deficit or a combined water and sodium deficit where the water losses exceed the sodium losses. Hypernatremia secondary to a water deficit arises in the setting of inadequate access to water or some impairment in ADH release or response. It is uncommon to see hypernatremia secondary to poor water intake except in infants or young children who cannot get water for themselves in response to their sense of thirst [79]. As for ADH-related anomalies, there are many causes of central or nephrogenic diabetes insipidus [80]. Again, given normal access to water, it is rare for the older child to develop hypernatremia even with impairment in the ADH axis because of the strong drive to drink in response to thirst [81]. In very young children with diabetes insipidus, however, the issue of access to water arises and hypernatremia may be a concern. Such hypernatremia can also be seen in the postoperative state in children with concentrating defects who are not allowed to drink by mouth and who are receiving a prescribed volume of fluid based on a presumed ability to concentrate urine and conserve water.

The most common etiology of hypernatremia in children is the loss of hypotonic fluid, which is fluid with a relative excess of water for its sodium content. In these situations, the total body water is decreased more than the total body sodium. The usual clinical scenario leading to such a condition is viral diarrheal illness with poor water intake or persistent vomiting. In this condition, there is loss of stool with sodium content typically <60 mEq/L. These children tend to excrete small volumes of concentrated urine with urine sodium content <20 mEq/L, underscoring the fact that they are conserving both water and sodium. Their hypernatremia is not a manifestation of a

total body excess of sodium but a depletion of sodium that is overshadowed by a larger relative depletion of body water. Therapy is aimed at restoring water and sodium balance by providing back the hypotonic fluid which was initially lost either by the use of intravenous saline solutions or with oral electrolyte therapy.

Fluid Replacement Therapy

Most commonly, the primary goal of fluid replacement therapy is restoration of an adequate effective circulating volume. In its absence, significant metabolic derangements can occur that then exacerbate perturbations in fluid and electrolyte homeostasis. The volume of fluid replacement required varies with the extent and etiology of the compromised circulation. In many children with acute illness, there may be an element of decreased effective volume that is mild and difficult to appreciate by clinical examination. Expansion of extracellular volume with infusion or ingestion of 20–40 ml/kg of fluid over a few hours often results in better perfusion and improved clinical appearance from presentation. Urine output tends to remain normal in these situations speaking against persistent non-osmotic ADH activity that would encourage volume overload [29].

Children with mild dehydration, up to about 5 % weight loss, will usually respond to the provision of 30–50 ml/kg of fluid over several hours

with marked clinical improvement. In the setting of more significant compromise of effective volume such as with loss of vascular tone in sepsis or a systemic inflammatory response, more than 200 ml/kg may be needed to achieve hemodynamic stability and effective perfusion. In most situations other than outright shock, the clinician can approach fluid resuscitation with either intravenous or oral rehydration therapy.

Assessment of Volume Depletion

In estimating the severity of dehydration, a change in weight from baseline is the best objective measure [82]. As rehydration proceeds, following weights on a serial basis becomes an important adjunct in assessing the efficacy of fluid repletion. If no baseline weight is known, most clinicians use various parameters based on history and physical examination to judge the severity of dehydration (Table 6). Children with mild dehydration will have few clinical signs and only a modest decline in urine output. As dehydration becomes more significant, classic findings such as dry mucous membranes, tenting skin, sunken eyes, and lethargy become prominent. With profound dehydration, there is anuria, marked alterations in consciousness, and hemodynamic instability.

Without access to prior weight values, most clinicians find it difficult to estimate accurately the degree of dehydration when it is mild or moderate. A capillary refill time greater than 2 seconds has

Table 6 Clinical assessment of dehydration

	Degree of dehydration		
	Mild	Moderate	Severe
Vital signs			
Pulse	Normal	Rapid	Rapid and weak
Blood pressure	Normal	Normal to slightly low	Shock
Weight loss			
Infant	<5 %	10 %	>15 %
Older child	<3 %	6 %	>9 %
Mucous membranes	Tacky	Dry	Parched
Skin turgor	Slightly decreased	Decreased	Tenting
Eye appearance	Normal tearing	Decreased tearing ± sunken	No tears + very sunken
Capillary refill	Normal	Delayed (>3 s)	Very delayed (>5 s)
Urine output	Decreased	Minimal	Anuric

long been touted as a useful physical finding suggesting effective volume depletion [83]. Unfortunately, delayed capillary refill is neither a sensitive nor specific marker of dehydration [84, 85]. It may be most useful if normal, as this does seem to exclude reliably severe dehydration. In a prospective cohort study of dehydrated children between 3 and 18 months of age, the best correlation between clinical assessment of degree of dehydration and actual volume depletion came in children who had obvious clinical parameters of significant dehydration such as prolonged skinfold tenting, a dry mouth, sunken eyes, and altered sensorium [86]. Similarly, in a review of preschool children with dehydration, the best clinical indicators of volume depletion – decreased skin turgor, poor peripheral perfusion, and Kussmaul breathing – accompanied more significant dehydration where there was little clinical question of volume depletion [87].

A study of 97 American children given intravenous fluids for rehydration in an emergency department underscored the difficulty in assessing even severe dehydration by standard clinical approaches [88]. Physicians' initial estimate of dehydration compared to the actual percent loss of body weight varied dramatically, with a sensitivity of 70 % for severe dehydration (>10 % loss) but only 33 % for moderate dehydration (6–10 % loss). This study suggested that adding a serum bicarbonate level to the assessment may be useful, increasing the sensitivity of the clinical scales to 100 % in severe dehydration and 90 % in moderate dehydration if both clinical features and a serum bicarbonate <17 mEq/L were found.

Other studies have found that laboratory studies by themselves are poor indicators of dehydration. In 40 children receiving intravenous fluids for dehydration, serum BUN, creatinine, uric acid, anion gap, venous pH, venous base deficit, urinary specific gravity, urinary anion gap, and fractional excretion of sodium were all assessed from prehydration blood and urine samples. Only the serum BUN/Cr ratio and serum uric acid significantly correlated with increasing levels of dehydration, but both lacked sensitivity or specificity for detecting more than 5 % dehydration [89]. Similarly, in a retrospective review of 168 dehydrated children, elevated serum urea levels and depressed serum bicarbonate levels were found to be useful adjuncts to clinical evaluation in accurately assessing the degree of dehydration but were not by themselves predictive [90].

In fact, with viral gastroenteritis, the most common cause of dehydration in children, there rarely is a significant laboratory anomaly despite clinically detected volume depletion, as underscored by the report of a cohort of children from the United Kingdom admitted for rehydration due to viral gastroenteritis in which only 1 % had an electrolyte derangement [91–93].

In children with volume depletion accompanying trauma, sepsis, surgery, or underlying renal dysfunction, it would be more likely to find perturbations in electrolyte and acid–base status. Thus, in the absence of a straightforward case of mild to moderate diarrheal dehydration, it is general consensus that blood should be obtained for assessment of electrolytes, bicarbonate, and renal function to help guide specific fluid and electrolyte therapy [94, 95].

As the child is volume resuscitated, it is important to reassess the child's clinical status. Initial estimates of degree of dehydration may need to be adjusted if the child is not showing progressive improvement. Most clinicians follow parameters such as general appearance and sensorium, change in weight from initiation of rehydration, and urine output and urine osmolality. In children with some types of renal dysfunction, there may often be an underlying chronic urinary concentrating defect. In these children, relatively dilute urine flow may be maintained even in the face of clinical dehydration and markers other than urine output and osmolality should be followed.

Oral Rehydration Therapy

Although oral rehydration with electrolyte solutions is a safe, convenient, and effective way to treat volume depletion, parenteral fluid and electrolyte therapy has been the mainstay of treatment for most children presenting with fluid and electrolyte imbalances [96–99]. Especially underutilized in North America, oral therapy has proved successful in clinical settings worldwide

in resuscitating children of all ages with profound fluid and electrolyte anomalies. Short of significant circulatory compromise, oral rehydration can be used as first-line therapy in all fluid and electrolyte aberrations [100, 101]. An example of a situation calling for oral rehydration is the following clinical scenario:

A healthy 4-year-old girl presents to her pediatrician's office following 3 days of a febrile illness. Her appetite has been severely depressed and her parents estimate that she has only had a few cups of fluid in the last 12 h. She has vomited once daily. She has continued to urinate, although less frequently and with smaller volumes. On physical examination, the girl looks unhappy but nontoxic and alert. Her pulse is 100 beats per minute and her sitting blood pressure is 80/50 mmHg. She will not cooperate with attempts at orthostatic vital signs. Her mucous membranes are somewhat dry and her weight today is 15 kg, exactly the same as her weight at a well child examination 6 months previously. The parents are concerned that she looks dehydrated.

Primary care and emergency department physicians face such clinical scenarios daily. Otherwise healthy children with viral illness causing mild to moderate dehydration will frequently be treated by intravenous fluids with the contention that oral rehydration will be too labor intensive or will take too much time. In fact, these children are excellent candidates for oral rehydration, and, in most developed countries where there is little concern for cholera-like enteritis, oral solutions with sodium contents from 30 to 90 mEq/L have been shown for years to be efficacious for rehydration [102–105].

With this girl, given the history and physical examination, it is unlikely that any clinically significant electrolyte perturbations will be found, so there is little indication for assaying electrolytes or renal function prior to starting oral rehydration [91–93]. The family is given a commercially available oral rehydration solution containing 75 mEq/L Na, 20 mEq/L K, 30 mEq/L citrate, and 2.5 % glucose. They are asked to provide 1 l of fluid (50 ml/kg) to the child over the next 4 h. The child should be offered small aliquots of fluid very often – 5 mls every 1–2 min at initiation.

If this regimen is tolerated with no vomiting, the aliquots may be gradually increased in volume and the frequency reduced, aiming to deliver at least the prescribed total volume over about 4 h. After her rehydration, the child should subsequently continue to be provided free access to fluid and resume an age-appropriate diet. If, on the other hand, there are any further episodes of vomiting, then for each episode of emesis, an additional 120–240 ml of oral rehydrating solution should be given, again with the goal to complete rehydration and resume usual fluid intake and nutrition.

The initial provision of oral fluid given often in small volumes is far more likely to be well tolerated by the dehydrated child than larger aliquots. If families are unwilling to provide the fluid in this manner, a nasogastric tube may be placed for continuous infusion of rehydrating solution.

Although occasional children may fail this approach and require intravenous rehydration, most children with mild to moderate rehydration can be rehydrated orally. A guide for the volumes of fluid to provide and the duration of rehydration can be found in Table 7.

The first oral rehydration solutions were developed in the 1940s at academic medical centers. Within 10 years, a commercial preparation formulated as a powder to be mixed with water was available, but its use became associated with an increased incidence of hypernatremia [106]. Several factors contributed to the development of this problem: the preparation was sometimes incorrectly administered as the powder itself or improperly diluted with too little water; when correctly reconstituted, the solution had a final carbohydrate concentration of 8 % predisposing to an osmotic diarrhea; and it was a common practice at that time for parents to use high solute fluids such as boiled skim milk as an adjunctive home remedy. Taken together, these early experiences contributed to reluctance by many clinicians to use oral rehydration solutions, especially since intravenous rehydration was becoming more standard in practice.

Over time, there came to be a better understanding of the physiology of water and solute absorption from the gut. Of prime importance

Table 7 Oral rehydration for previously healthy, well-nourished children

Type of dehydration	Rehydration phase	Rehydration duration	Replacement of ongoing losses	Nutrition
Mild (<5 %)	30–50 ml/kg ORT	3–4 h	60–120 ml ORS for each diarrheal stool or episode of emesis[a]	Continue breast milk or resume age-appropriate usual diet
Moderate (5–10 %)	50–100 ml/kg ORT	3–4 h	As above	As above
Severe (>10 %)	100–150 ml/kg ORT	3–4 h	As above with use of nasogastric tube if needed	As above
Evidence of shock	20 ml/kg 0.9 % NaCl or lactated Ringer's IV	Repetitive infusions until perfusion restored then transition to ORT 100 ml/kg over 4 h	As above with use of nasogastric tube if needed or consideration of further IV therapy	As above
Accompanying hypernatremia	Per type of dehydration	At least 12 h for ORT	As above	As above
		Monitor fall in serum Na		

ORT oral rehydration therapy with fluid containing 45–90 mmol/l Na, 90 mmol/l glucose, 20 mmol/l K, and 10–30 mmol/l citrate
IV intravenous infusion
[a]For children >10 kg, aliquots for replacement of ongoing losses should be doubled to 120–240 ml rehydration solution for each stool or emesis

was the recognition that many substances actively transported across intestinal epithelium had an absolute or partial dependence on sodium for absorption and that sodium itself was actually better reabsorbed in their presence [107–109]. Moreover, it became clear that the sodium/glucose cotransporter remained intact not only in the face of enterotoxic gastroenteritis such as seen with cholera or Escherichia coli but also in more common viral and bacterial enteritides [100, 101]. This led to the routine introduction of glucose into oral rehydration solutions in a fixed molar ratio of no more than 2:1 with sodium.

The World Health Organization (WHO) and the United Nations Children's Fund champion the use of a rehydrating solution that includes Na 90 mmol/L, Cl 80 mmol/L, K 20 mmol/L, base 30 mmol/L, and glucose 111 mmol/L (2 %). This WHO solution has proved useful in many pediatric clinical trials and has also been shown to reduce the morbidity and mortality associated with diarrheal illness regardless of its etiology [102, 103], although it may not be readily commercially available in many locales.

Most commercially available oral rehydration solutions have somewhat higher carbohydrate content, a lower sodium content, and a higher carbohydrate to sodium ratio than WHO solution (Table 8). Some preparations are available as powder and other as ready-to-drink formulations. Some manufacturers have also used rice solids as a carbohydrate source instead of glucose.

Many of these formulation changes arose from concerns that using an oral rehydrating solution with a sodium content >60 mmol/L would prove problematic in developed countries where most gastroenteritis is viral in nature and has a lower sodium content than the secretory diarrheas seen in less developed areas. Some feared that minimally dehydrated children losing small amounts of sodium in their stools would become hypernatremic if exclusively provided WHO solution and a few studies did document such iatrogenic hypernatremia [110]. Subsequently, solutions with sodium content ranging from 30 to 90 mmol/L have proved quite effective in cases of mild dehydration stemming from causes other than secretory diarrhea [104, 105, 111]. A meta-analysis of studies focused on the safety and efficacy of oral rehydration solution in well-nourished children living in developed countries documented *little* evidence that WHO solution was more likely to cause aberrations in serum sodium than lower sodium containing oral

Table 8 Oral rehydration solutions

Product	Concentration, mmol/L					
	Na	Sugar	K	Cl	Base	Osmolarity (mOsm/L)
WHO ORS[a]	90	111	20	80	30	311
CeraLyte 90[a]	90	220[b]	20	80	30	275
Low-Na ORS[a]	75	75	20	65	30	245
Rehydralyte	75	140	20	65	30	300
CeraLyte 70[a]	70	220[b]	20	60	30	230
CeraLyte 50[a]	50	220[b]	20	40	30	200
CeraLyte 50 lemon	50	170[b]	20	40	30	200
Enfalyte	50	170	25	45	34	167
Pedialyte	45	140	20	35	30	254

[a]Provided as powder. Needs to be reconstituted with water
[b]Contains rice syrup solids substituted for glucose

Table 9 Composition of common oral fluids[a]

Fluid	Na (mEq/L)	K (mEq/L)	Source of base	Carbohydrate (g/100 ml)
Apple juice	<1	25	Citrate	12
Orange juice	<1	55	Citrate	12
Milk	20	40	Lactate	5
Cola	2	<1	Bicarbonate	10
Ginger ale	4	<1	Bicarbonate	8
Kool-Aid	<1	<1	Citrate	10
Gatorade	20	2.5	Citrate	6
Powerade	10	2.5	Citrate	8
Jell-O	25	<1	Citrate	14
Coffee	<1	15	Citrate	<0.5
Tea	2	5	Citrate	10

[a]Adapted in part from data found in Feld et al. [113]

rehydration solutions [112]. Why ingestion of lower tonicity oral rehydration fluids would be less problematic than infusion of similar tonicity intravenous fluid is not clear, but does again underscore the safety of oral rehydration.

Oral Rehydration with Fluids Other Than ORS

Despite the efficacy and availability of commercial oral rehydration solutions and the ease with which other electrolyte solutions can be mixed at home with recipes requiring few ingredients other than water, sugar, and salt, many children are still given common household beverages for rehydration instead of oral rehydration solutions. In children with dehydration and electrolyte losses from vomiting or diarrhea, most common beverages do not contain adequate sodium or potassium supplementation, and the base composition and carbohydrate source are also often suboptimal (Table 9). Similarly, most sports drinks for "rehydration" following exercise are also depleted of sufficient electrolytes for gastrointestinal disease given sweat is many fold lower in electrolyte composition than gastrointestinal fluid. In prescribing oral rehydration to children in an ambulatory setting, the clinician should specify the appropriate fluid and volume for the child to ingest, emphasizing the need to use a fluid with appropriate electrolyte content if there is concern about evolving imbalances in sodium, potassium, or bicarbonate homeostasis.

Oral Rehydration and Serum Sodium Abnormalities

Although oral rehydration is often considered for children with modest dehydration and no presumed electrolyte anomalies, oral rehydration with WHO or WHO-like solution has also been used in cases of dehydration accompanied by hyponatremia or hypernatremia [114, 115]. Although most children with severe hypernatremia (>160 mEq/L) can be successfully rehydrated orally, there have been reports of seizures, generally as a result of too rapid correction of serum sodium from the provision of supplemental water along with the glucose–electrolyte solution [114, 115]. In those cases, the average serum sodium fell by 10–15 mEq/L over 6 h rather than over 24 h as advised. In follow-up studies, no seizure activity was seen in a similar cohort of hypernatremic children who received 90 mmol/L Na rehydration solution alone at a rate calculated to replace the infant's deficit over 24 h [114]. It is important for the practitioner to remember that once peripheral perfusion has been stabilized with initial volume expansion, there is no benefit to correcting any deficit rapidly and taking 24–48 h may be a more prudent course in the face of significant electrolyte anomalies.

Oral Rehydration Schemes

Several oral rehydration schemes have been shown to be quite effective and well tolerated. In one approach used extensively in developing countries, the patient's volume deficit is calculated on the basis of weight loss and clinical appearance [116]. The volume deficit is doubled and this becomes the target rehydration volume to be given over 6–12 h. Two-thirds of this volume is given as a glucose–electrolyte solution containing 90 mmol/L Na over 4–8 h; once this has been ingested, the remaining volume is provided as water alone over 2–4 h. In cases of suspected or confirmed hypernatremia with serum sodium exceeding 160 mEq/L, the volume deficit would not be doubled and would be administered as 90 mmol/L Na glucose–electrolyte solution alone over 12–24 h. Patients who refuse to take

fluids by mouth have nasogastric tubes placed. With this approach, successful oral rehydration is the rule and 95 % of children are fully rehydrated without the need for intravenous therapy.

An alternative approach has been to have the child begin by taking 15 ml/kg/h of a 60–90 mmol/L Na rehydration solution by mouth or nasogastric tube [117]. The solution is given in small frequent quantities and increased up to 25 ml/kg/h until hydration has improved at which point solid feedings are reintroduced and volumes of 5–15 ml/kg of rehydration solution offered after feeds until the volume deficit have been delivered.

Over two decades ago, the American Academy of Pediatrics issued guidelines for the treatment of fluid and electrolyte deficits with oral rehydration solutions [100]. Children with acute dehydration and extracellular volume contraction were to be provided 40–50 ml/kg of a glucose–electrolyte solution containing in each liter 75–90 mmol Na, 110–140 mmol glucose (2–2.5 %), 20 mmol potassium, and 20–30 mmol base. This volume was to be administered over 3–4 h and then once there has been amelioration of the extracellular volume contraction; the child would be changed to a maintenance solution with 40–60 mmol/L Na at half the rate. If the child was still thirsty on this regimen, there should be free access to supplemental water or low-solute fluid such as breast milk.

Based on much of this published clinical experience, an evidence-based guideline for treating dehydration in children from industrialized European countries was created in the late 1990s, recommending oral rehydrating solution containing 60 mmol/L of sodium, 90 mmol/L of glucose, 20 mmol/L of potassium, and 10–30 mmol/L of citrate with rehydration occurring over 3–12 h utilizing from 30 to 150 ml/kg of fluid depending on the degree and type of dehydration [82].

In 2004, the American Academy of Pediatrics updated its oral rehydration recommendations and endorsed guidelines promulgated by the Center for Disease Control and Prevention [118, 119]. Minimal dehydration in children weighing

less than 10 kg was to be treated with provision of 60–120 ml of oral rehydration fluid for each watery stool or each episode of vomiting. In larger children, twice this volume would be provided. For children with more moderate dehydration, 50–100 ml/kg of oral rehydration solution would be given over 2 to 4 h to account for estimated fluid deficit, and ongoing losses would be treated with the 60–240 ml per stool or emesis depending on size. Nursing babies would continue to receive breast milk as desired and formula-fed babies would be provided age-appropriate diet as soon as they had been rehydrated. For severely dehydrated children, a combination of intravenous hydration with isotonic fluids and prompt transition to oral rehydration solution by mouth or nasogastric tube was recommended. Overly restricted diets were to be avoided during gastrointestinal illness and attention to adequate caloric intake emphasized (see Table 7).

Use and Acceptance of Oral Rehydration Solutions

Despite the availability of guidelines for oral rehydration and their endorsement by professional organizations, oral rehydration solutions continue to be underutilized by clinicians in both the developed and undeveloped world [104, 120]. Even in Bangladesh where oral rehydration has been closely studied and championed by both local and international medical agencies for decades, its use is still suboptimal [121, 122]. Some studies do suggest that familiarity with a specific scheme for oral rehydration increases its use in the emergency department and that younger graduates of training programs are more likely to use oral rehydration for advanced cases of clinical dehydration than their older colleagues, even when there was no generational difference in the baseline knowledge of published data in this field or acceptance of its validity [123].

When utilized according to recommendation, oral rehydration has been demonstrated to be almost universally successful in achieving some degree of volume repletion [10]. Other advantages to oral therapy include the stability of the product despite lengthy shelf storage, its ability to be administered readily by the child's caretaker in nearly any locale, and avoidance of the discomfort and potential complications associated with intravenous catheter placement [124]. In developed countries, there has been the concern that some powdered ORS formulations may not be looked upon by parents as convenient since they must be mixed with water prior to provision, but a randomized controlled trial comparing an urban pediatric clinic and a suburban medical practice found that parents were equally satisfied with the ease and effectiveness of a powdered solution as a commercially prepared ready-to-drink solution [125].

Oral rehydration is somewhat less successful in hospitalized children than in children treated in an ambulatory setting [10]. This difference may be directly related to the degree of dehydration or other complicating clinical issues leading to hospital admission. Moreover, the relatively labor-intensive slower approach to oral rehydration may be problematic in medical facilities with time constraints or space limitations [124, 126].

Frozen-flavored oral rehydration solutions may be more readily accepted than conventional unflavored liquid electrolyte solutions. Their use resulted in higher rates of successful rehydration in children with mild to moderate dehydration, even if these children initially failed conventional oral rehydration [124]. Frozen-flavored rehydration solution is now commercially available in many parts of the world, as is a variety of flavored rehydration solutions.

Another potential issue with oral rehydration is that its use does not alter the natural course of the child's illness. For instance, in gastroenteritis with dehydration, by far and away the most common illness requiring rehydration in children, oral rehydration does not lower stool output or change the duration of diarrheal illness [127]. As a result, caretakers may abandon oral rehydration because the child continues to have symptoms, failing to appreciate the benefits of ongoing hydration. Oral rehydrating solutions have been formulated with lower electrolyte composition and different carbohydrate moieties with the goal to reduce the osmolarity of solutions and potentially augment fluid absorption from the small intestine [112].

The rice-based oral solutions have been studied most extensively. In these solutions, glucose is substituted with 50–80 g/l of rice powder. In a meta-analysis of 22 randomized clinical trials comparing rice-based solution to conventional glucose-containing solutions, stool output dramatically decreased in children with cholera given rice-based hydration but did not change in children with other bacterial or viral enteritides [128].

There are some reports that suggest that providing children with non-cholera enteritis with reduced osmolarity rehydration solution may be beneficial. A study of 447 boys less than 2 years of age admitted for oral rehydration compared WHO solution (osmolarity 311 mmol/l) and a solution containing less sodium and chloride (osmolarity 224 mmol/l). Children who received the lower osmolarity solution had reduced stool output, reduced duration of diarrhea, reduced rehydration needs, and reduced risk of requiring intravenous fluid infusion after completion of oral hydration [129]. A meta-analysis of nine trials comparing WHO solution to reduced osmolarity rehydration solution concluded that children admitted for dehydration had reduced needs for intravenous fluid infusion, lower stool volumes, and less vomiting when receiving the reduced osmolarity solution [130].

Intravenous Therapy

Although absolute indications for parenteral intravenous therapy are limited, they do include significantly impaired circulation or overt shock. In addition, there are occasional children who are truly unable to sustain an adequate rate of oral fluid intake despite concerted effort or have such persistent losses that parenteral therapy comes to be necessary. The mainstays of fluid therapy in children are saline or buffered saline crystalloid solutions. Isotonic versions of these crystalloids are used for volume resuscitation and hypotonic saline solutions may be used in addition to provide supplemental maintenance hydration. In addition to crystalloid solutions, there are several colloid fluids that are also used by many clinicians. Table 10 lists the electrolyte content of some of the more common intravenous solutions used for pediatric fluid therapy.

Choice and Volume of Parenteral Fluid

Children with significant extracellular volume contraction (greater than 10 % acute weight loss in an infant or 6 % weight loss in an older child) should receive an isotonic crystalloid solution such as 0.9 % saline (154 mEq/L NaCl) or lactated Ringer's (130 mEq/L NaCl) at a rate of 20 ml/kg over 30–60 min. In some children, even more rapid infusions or serial provision of such aliquots may be necessary to restore effective volume. Children with less pronounced dehydration may not exhibit signs or symptoms of volume contraction. In certain situations, however, it may be clinically warranted to provide them with an initial rapid intravenous bolus to initiate rehydration therapy.

Concomitant with the placement of intravenous access, blood should be obtained for determination of serum electrolytes, osmolality, and renal function. Given that dehydrated children often have high levels of vasoactive hormones and high vasopressin levels, it is most prudent to establish baseline electrolyte levels since it is possible to alter electrolyte balance rapidly with intravenous therapy. In the face of inadequate tissue perfusion, a parenteral fluid infusion should begin immediately prior to the return of any pertinent laboratory results. If hemorrhagic shock is suspected, resuscitation with packed red blood cells is optimal. In cases of severe volume depletion, if the child does not improve with the initial 20-ml/kg crystalloid bolus, this should be repeated up to two additional times. In children who have not improved despite administration of 60 ml/kg of total volume over an hour or in children in whom underlying cardiac, pulmonary, or renal disease may make empiric aggressive rehydration more problematic, consideration should be given to placement of a central monitoring catheter to more accurately assess intravascular volume and cardiac dynamics [131]. In some instances of profound ineffective circulating volume, such as might accompany certain cases of sepsis, initial volume resuscitation may require sequential infusions of fluid ultimately exceeding 100 ml/kg.

Within minutes of infusion of a crystalloid fluid, it becomes distributed throughout the extracellular space. Since this involves equilibration of

Table 10 Composition of common intravenous fluids

Fluid	Osmolarity (mOsm/l)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)	Buffer (source) (mEq/l)	Mg (mEq/l)	Ca (mEq/l)	Dextrose (g/l)
Crystalloids								
0.9 % saline	308	154	0	154	0	0	0	0
Lactated Ringer's	275	130	4	109	28 (lactate)	0	3	0
D5 0.45 % saline	454	77	0	77	0	0	0	50
D5 0.22 % saline	377	38	0	38	0	0	0	50
5 % dextrose water	252	0	0	0	0	0	0	50
Normosol	295	140	5	98	27 (acetate) 23 (gluconate)	3	0	0
Plasma-Lyte	294	140	5	98	27 (acetate) 23 (gluconate)	3	0	0
Colloids								
5 % albumin	309	130–160	<1	130–160	0	0	0	0
25 % albumin	312	130–160	<1	130–160	0	0	0	0
Fresh frozen plasma	300	140	4	110	25 (bicarbonate)	0	0	0
3.5 % Haemaccel	301	145	5	145	0	0	6	0
6 % hetastarch	310	154	0	154	0	0	0	0
Dextran 40 or 70	310	154	0	154	0	0	0	0

the fluid between the two components of the extracellular space – the intravascular and interstitial spaces – actually only one-third to one-quarter of infused crystalloid stays in the blood vessels [132]. This accounts for the need to give large volumes of crystalloid in the setting of circulatory collapse and leads some to suggest that colloid solutions such as 5 % or 10 % albumin should play a role in resuscitation [133, 134].

Colloid Solutions and Volume Resuscitation

The use of colloid solutions for volume resuscitation is controversial. Colloids were once included in a number of widely promulgated guidelines for the care of patients in emergency facilities and intensive care units both for hemorrhagic shock prior to the availability of blood and for nonhemorrhagic shock as an adjunct to crystalloid use [135]. Types of colloid utilized included 5 % albumin, fresh frozen plasma, modified starches, dextrans, and gelatins. These guidelines, generally aimed towards the fluid resuscitation of adults, were composed despite the prior publication of a systematic review of randomized controlled trials that demonstrated no effect on mortality rates when colloids were used in preference to crystalloids [136]. Moreover, there is a distinct cost disadvantage to using colloid solutions.

Subsequent systematic reviews have looked at this issue anew. In one meta-analysis of 38 trials comparing colloid to crystalloid for volume expansion, there was no decrease in the risk of death for patients receiving colloid [135]. In the other review, albumin administration was actually

shown to increase mortality by 6 % compared to crystalloid [137]. Proposed mechanisms contributing to this worse outcome include anticoagulant properties of albumin [138] and accelerated capillary leak [139].

A drawback of all these systematic reviews, however, has been the limited number of studies that included children other than ill premature neonates. As a result, generalization of these results from ill adults may not be germane to all critically ill volume-depleted children. For instance, a report of 410 children with meningococcal disease suggests that albumin infusion in this population may not have been harmful, as case fatality rates were lower than predicted [140]. Overall, however, there seems to be no substantive data to support the routine use of colloid to complement or replace crystalloid in fluid resuscitation. Rather, repetitive infusions of large volumes of crystalloid seem to be well tolerated in volume-depleted children, do not seem to predispose to excessive rates of acute respiratory distress syndrome or cerebral edema, and in some conditions, such as sepsis, play an important role in improved survival [141]. A recent survey of pediatric anesthesiologists in Western Europe reported that colloid solutions are being used less frequently in infants and older children and suggested that familiarity with some of the issues raised in these systematic reviews are affecting practice patterns [142].

Repetitive infusions of crystalloid may also prove problematic in some children. Most notably, if very large volumes of 0.9 % NaCl are used acutely for volume resuscitation, it is not unusual for children to develop a hyperchloremic metabolic acidosis. This occurs as acidotic peripheral tissues begin to reperfuse and already depleted extracellular bicarbonate stores are diluted by a solution with an isotonic concentration of chloride [131, 143]. This acidosis can be ameliorated by supplemental doses of bicarbonate as well as the addition of supplemental potassium as needed. There is sometimes a tendency for clinicians to react to the hyperchloremic metabolic acidosis with further saline bolus infusions. In the face of corrected hypoxia or hypovolemia, however, such maneuvers may only exacerbate the chloride-driven acidosis [144]. This hyperchloremic acidosis is seen less frequently when Ringer's lactate solution is used as the resuscitation fluid because of the metabolic conversion of lactate to bicarbonate. In the setting of significant preexisting acidosis or underlying hepatic dysfunction preventing the metabolism of lactate, infusion of Ringer's lactate solution may, however, exacerbate an acidosis.

With the recent suggestion that some children with acute illness or following surgery may benefit from a prolonged period of isotonic fluid infusion given high levels of ADH and the possibility for hyponatremia developing with hypotonic fluid therapy, some have expressed concern that a hyperchloremic acidosis may develop in these children. In a prospective randomized study of more than 100 children with gastroenteritis given isotonic intravenous rehydration and maintenance therapy, there was no tendency for the development of hyperchloremic acidosis even after a day of isotonic fluid provision. Although serum chloride levels did tend to increase in these children, serum bicarbonates also improved, potentially related to improved effective volume and subsequent better tissue perfusion [145]. Similarly, in children who underwent cardiac surgery who were given isotonic solutions for their maintenance fluid needs, although there was a tendency for a hyperchloremic acidosis to develop, there seemed to be no significant clinical ramifications and long-term outcomes were similar to children who did not develop hyperchloremic acidosis [146].

Large volume infusion of blood may also predispose to electrolyte anomalies as well as manifestations of citrate toxicity. If aged whole blood is infused, there is the possibility that a large potassium load will be delivered to the patient as potassium may have moved from less viable erythrocytes into the plasma. Since most patients receive packed red blood cells instead of whole blood, this potential problem is minimized, and the potassium in the small volume of plasma in a packed cell transfusion can generally be accommodated by intracellular uptake.

Citrate is used as the anticoagulant in stored blood. Since citrate complexes with calcium, there

can be a fall in ionized calcium levels if large volumes of citrate-containing blood are infused rapidly or if there are concomitant perturbations in calcium homeostasis. Similarly, citrate may complex with magnesium and magnesium depletion may occur. The liver usually metabolizes infused citrate into bicarbonate and alkalosis can also occur if large volumes of citrate are delivered. In the setting of hepatic dysfunction, however, citrate will not be metabolized and serves as an acid load and will help create an acidosis or exacerbate any underlying acidosis.

Regardless of the initial infusion with either colloid or crystalloid, once sufficient volume to restore circulatory integrity has been infused, less rapid volume expansion is necessary. During this phase, the rapidity of fluid repletion is most probably not a concern unless there are severe underlying aberrations in the serum sodium or serum osmolality. In the absence of these derangements or profound volume deficit, if the child has improved significantly with the initial parenteral volume expansion, attempts should be made to reinstitute oral rehydration. Prolonged intravenous therapy should be rarely necessary.

Rapid Rehydration

In an attempt to minimize the duration of hospital-based care, a scheme of rapid intravenous resuscitation and follow-up oral rehydration has been adopted by many pediatric emergency departments to treat children with up to 10 % dehydration secondary to vomiting and gastroenteritis [147]. After infusion of 20–30 ml/kg of intravenous crystalloid, the child is allowed to take up to several ounces of a standard oral rehydration fluid, and if this intake is tolerated without vomiting for 30–60 min, then the child discharged home to continue rehydration, initially with a prescribed volume of standard rehydration solution.

If the child does not tolerate oral rehydration or if there are such significant electrolyte anomalies that there are concerns regarding potential adverse CNS sequelae of too rapid rehydration, then intravenous rehydration may be the best route for continued hydration. Children who have had

very sudden fluxes in electrolytes may become symptomatic earlier. On the other hand, children whose severe sodium abnormalities are thought to be more chronic in nature must be treated in a more controlled fashion since they are at higher risk for developing CNS symptoms during treatment.

The vast majority of children treated in emergency facilities for volume repletion do well with such rapid rehydration. These children are generally healthy with normal cardiac and renal function and have developed extracellular volume depletion relatively rapidly. As a result, they suffer no ill effects from rapid rehydration. In fact, the clinical success of this aggressive restoration of extracellular volume underlies the calls to reexamine or abandon the traditional deficit therapy approach to rehydration with its tedious calculations of fluid and electrolytes losses and requirements, especially in the setting of otherwise healthy children who are acutely ill [9, 148].

Symptomatic Hyponatremia

In the setting of symptomatic hyponatremia, especially if the child has seizures, it is important to raise the serum sodium concentration by approximately 5 mEq/L in an urgent fashion. Generally, this results in stabilization of the clinical situation and allows for further more considered evaluation and treatment of the child. This is one of the few situations in which hypertonic saline (3 % NaCl, 514 mEq/L) should be utilized.

To calculate the proper volume of 3 % saline to infuse, the child's TBW must be multiplied by the 5 mEq/L desired increase in serum sodium to determine the amount of sodium (in mEq) to infuse. Since every ml of 3 % saline contains 0.5 mEq of sodium, doubling the number of mEq of sodium needed results in the proper milliliter volume of 3 % saline to infuse. Thus, in the 20-kg child, the TBW is approximately 12 L (0.6 L/kg $\times$ 20 kg) and the desired sodium dose would be 60 mEq (12 L $\times$ 5 mEq/L). If 120 ml of 3 % saline were infused, the serum sodium concentration would be expected to rise by approximately 5 mEq/L. The infusion should be

given at a rate to increase the serum sodium by no more than 3 mEq/L/h and is often given more slowly over the course of 3–4 h [149]. If the child continues to be symptomatic from hyponatremia after this infusion, additional 3 % saline may be given until the symptoms improve or the serum sodium is in the 120–125 mEq/L range. At that point, further correction of the hyponatremia should consist of a slower infusion of more dilute saline to cover the sodium deficit, the sodium maintenance needs, and any volume deficit. Consideration of the role of ADH and prior excess free water provision should also be considered in determining the volume and tonicity of fluid to be provided.

Asymptomatic Hyponatremia

If a child has severe hyponatremia but is not symptomatic, there is no need to administer hypertonic saline based solely on a laboratory anomaly. With or without symptoms, in cases of severe hyponatremia, the child should be carefully evaluated as to the etiology of the hyponatremia, keeping in mind that hyponatremia tends to result from an imbalance of water regulation. If this is the case, free water should be restricted and appropriate supplementation with intravenous saline solutions begun to provide maintenance sodium requirements of approximately 2–3 mEq/kg/day and any ongoing losses of sodium.

Besides these maintenance sodium needs, if the child has an element of dehydration, every kilogram of body weight lost from baseline represents a 1-L deficit of nearly normal saline from the total body water as well. These losses are often referred to as isotonic losses. These account for a sodium deficit of 154 mEq/L that also must be included in the calculations for sodium replacement.

In the setting of hyponatremic dehydration, there have been additional sodium losses as well. Generally, these occur as viral diarrheal stool losses with a sodium content ≤60 mEq/L are replaced with fluids with lower sodium concentration. To estimate these sodium losses, the difference between the child's desired serum sodium and current serum sodium is multiplied by the child's estimated TBW. This product represents the hyponatremic sodium losses that must be added to the maintenance sodium needs, any ongoing losses, and the sodium losses that accompanied weight loss. An example of the calculations and therapeutic maneuvers that need to be considered with significant hyponatremia is presented in the following case study:

A girl who normally weighs 10 kg suddenly develops generalized seizures and is brought by ambulance to the emergency department. She has had a week of gastroenteritis, has felt warm to touch, and has been drinking water and apple juice only, refusing any other liquids or any solid food for several days. Intravenous access is placed and lorazepam is administered and the seizure activity stops. The emergency department physician orders serum chemistries and the child is weighed and found to be 8.8 kg. A bolus infusion of 200 ml of 0.9 % NaCl is administered over the next 30–60 min after which the girl appears well perfused but she is still lethargic. The serum sodium is then reported to be 112 mEq/L. While further evaluation of the child's overall status is ongoing, it is important to begin correcting the symptomatic hyponatremia.

The child has actually already received approximately 30 mEq of sodium in the 0.9 % NaCl bolus given because of her dehydration and poor perfusion. Given her TBW of roughly 5.5 L (wt in kg × 0.6 L/kg), this should result in an increase in her serum sodium by approximately 5 mEq/L. Since the child has had hyponatremic seizures and is still exhibiting some central nervous system effect with her lethargy, it is prudent to raise the serum sodium by 5 mEq/L so that it will be in the 120–125 mEq/L range. Since she is hemodynamically stable, it is also best not to provide an excess of further volume until the child undergoes imaging to assess for cerebral edema, especially given the history of seizures, lethargy, and hyponatremia. By using a small volume of hypertonic saline, the serum sodium can be raised in a controlled manner while further evaluation of the child continues. It would take about 28 mEq of sodium (TBW × desired increase in serum sodium = 5.5 L × 5

mEq/L) to accomplish the desired elevation. Since each ml of 3 % saline contains about 0.5 mEq of sodium, a total of 56 ml of 3 % saline could be infused over approximately 3–4 h.

In addition to this acute management to restore initial circulation and perfusion and to raise the serum sodium to a safer level, plans must be formulated to attend to the patient's overall volume and sodium deficit. To prescribe the proper follow-up intravenous fluid, the patient's water and electrolyte deficits at presentation must be reconciled with her therapy thus far.

The child's water deficit is 1.2 l, reflecting the 1.2-kg weight loss. She has "maintenance" water needs of an additional 1 l/day based on her normal weight of 10 kg. She is having no other ongoing water losses and has already received nearly 250 ml in intravenous fluid in the form of 0.9 % NaCl and 3 % NaCl. Her current water needs are thus 1,950 ml.

The child's normal "maintenance" sodium needs are 30 mEq/day (3 mEq/kg/day). She has lost 1.2 kg of isotonic fluid in body weight that represents 185 mEq of sodium. In addition, she has hyponatremic sodium losses that have arisen as her diarrheal stool that contained sodium was replaced with water alone. To calculate these needs, her normal total body water needs to be multiplied by the difference in her serum sodium from a normal value of 135 mEq/L. Her TBW is 6 L (TBW = 0.6 L/kg × 10 kg) and the difference in serum sodium is 23 mEq/L (135 − 112 mEq/L); her hyponatremic losses are therefore 138 mEq (6 L × 23 mEq/L). Total sodium needs are thus 30 mEq of maintenance, 185 mEq of isotonic losses, and 138 mEq of hyponatremic losses or a total of 353 mEq. She has already received 52 mEq of sodium from the 400 ml of 0.9 % NaCl given in the emergency department. Her current sodium needs are thus just about 300 mEq.

To choose the proper solution for this child, the deficit of 1,950 ml of water should contain 300 mEq of sodium. This is best approximated by 0.9 % NaCl with its NaCl content of 154 mEq/L NaCl. In the past, it has been suggested that half of the fluid and sodium deficit be replaced over 8 h and the remainder over the ensuing 16 h. Although such a plan can be followed, there is little evidence that more rapid correction of the hyponatremia is harmful except if the patient has been symptomatic with hyponatremia or has profound asymptomatic hyponatremia of chronic duration. In these cases, it is safest to plan to correct the serum sodium by no more than 12–15 mEq/L over 24 h. More rapid correction has resulted in osmotic demyelination injury to the brain with devastating long-term neurologic outcomes [149–151].

Severe Hypernatremia

With hypernatremia, therapy is again guided by the clinical situation and provision of intravenous fluid is usually reserved for those children with very elevated serum sodium values who are not considered candidates for oral rehydration therapy. In cases of hypernatremia due to salt poisoning, there should be signs of overhydration and volume expansion. Excretion of sodium should be enhanced by using a loop diuretic to augment urine sodium losses and by replacing urine output with free water. If the patient has significant underlying renal or cardiac compromise, dialysis and ultrafiltration may be necessary to correct the water and electrolyte imbalance [77, 78]. With hypernatremia and volume expansion from salt excess, it will be detrimental to provide further intravenous saline.

In hypernatremia accompanied by volume loss, any significant alterations in effective circulation should be addressed with 20 ml/kg bolus infusions of an isotonic crystalloid solution until effective peripheral perfusion is restored. Then, further provision of water and sodium should be provided based on calculated water and sodium needs. In the majority of cases, with mild elevations in serum sodium and minimal degrees of dehydration, the actual calculation of deficits is probably unnecessary since the child will be hemodynamically stable and a candidate for exclusive oral rehydration. In situations where there is profound hypernatremia or circulatory compromise, it remains necessary, however, to

be able to calculate a free water deficit to tailor intravenous rehydration therapy. An example of such a situation is outlined in the following clinical scenario:

After 2 days of refusing to nurse, a 5-kg infant boy with a viral syndrome presents to an emergency department in shock, 15 % dehydrated with a weight of 4.25 kg and a serum sodium of 170 mEq/L. He receives 300 ml of 0.9 % NaCl urgently and further therapy is now planned.

The child has lost 750 g of weight. Since this is hypernatremic dehydration, there has been loss of water in excess to salt. Thus, part of the weight loss represents isotonic losses but a larger proportion represents free water loss. The child's free water deficit can be calculated by the equation

$$[(\text{serum Na actual})/(\text{serum Na desired})$$
$$\times \text{ total body water}] - \text{total body water}$$

Substituting the appropriate data for this baby,

$$[(170/145) \times (0.6 \times 4.25)] - (0.6 \times 4.25)$$
$$= [1.2 \times 2.55] - 2.55 = 0.51 \text{ L}$$

Thus, of this baby's 750-ml fluid deficit due to dehydration, 510 ml is free water and 240 ml is normal saline.

Too rapid correction of the baby's serum sodium with free water could result in cerebral edema as the water infused into the extracellular space follows osmotic forces and moves into the intracellular space. In cases of hypernatremia where the serum sodium exceeds 160 mEq/L, it is considered safest to correct the serum sodium by no more than 15 mEq/day. In this boy's case, this would mean that correction to a serum sodium in the normal range would take about 2 days.

If the fluid and electrolyte therapy must be given intravenously, the appropriate prescription again depends on calculation of water and sodium requirements and deficits. His original fluid deficit was 750 ml and his maintenance water needs are estimated at 500 ml/day. Thus, over the next 2 days, the fluid needed to replace the deficit and provide maintenance water is

about 1,750 ml. Of this volume, the baby has already received 300 ml of fluid in the emergency department so a net deficit of 1,450 ml now exists.

The baby has maintenance sodium needs of 15 mEq/day (3 mEq/kg/day). His sodium deficit reflects only the isotonic fluid losses that have been estimated above at 240 ml of normal saline or 37 mEq of sodium. Thus, over the next 2 days, his sodium needs are 67 mEq of which he has already received more than 45 mEq in the emergency department due to initial volume expansion.

Initiating an infusion of 30 ml an hour of free water should result in the slow and steady correction of the hypernatremia over 2 days by providing the nearly 1.5 l of free water that the child requires to replace losses and provide ongoing needs. The serum sodium should be monitored every 4 h initially, and if it is falling faster than desired (about 0.5 mEq/h), then the sodium should be added to the rehydration fluid.

Fluid and Electrolyte Therapy with Renal Dysfunction

Impact of Kidney Disease

Children with compromised renal function often manifest a reduced tolerance for changes in total body water as well as changes in the composition or distribution of volume between the intracellular and extracellular body spaces. Similarly, alterations in electrolyte balance are more likely problematic because normal homeostatic mechanisms are frequently perturbed. Especially in the child with marked nephrosis or significant impairment in renal clearance, it becomes vital to approach the provision of fluids and electrolytes with great care.

As far as fluid therapy is concerned, of utmost importance is the recognition that the concept of maintenance fluids or electrolytes presupposes normal renal function. Roughly two-thirds of any daily maintenance fluid prescription is to replace urinary water losses. Similarly, urinary electrolyte losses figure prominently in daily electrolyte balance. In the setting of oliguria or anuria,

provision of maintenance fluids could contribute to and, potentially, exacerbate volume overload, and maintenance electrolyte therapy could result in electrolyte anomalies.

Fluid and electrolyte needs of the child with renal dysfunction are better considered in the context of the child's current volume status and electrolyte needs. For instance, in symptomatic volume depletion with decreased circulatory perfusion, volume expansion would be initiated regardless of urine output. Once volume is repleted, the child's needs could be reassessed along with his current renal function. The child who is volume overloaded would best be managed by fluid restriction and provision of only insensible losses of approximately 300 ml/m^2. Insensible fluid losses should be considered essentially electrolyte free water. The child who is volume replete should be kept volume replete. This is most readily accomplished by providing a combination of insensible losses as free water and any other volume losses (urine output, diarrheal stool, surgical drain output, emesis) on an additional milliliter-for-milliliter basis. If there are significant ongoing losses from a single source, the electrolyte composition of this fluid can be assayed so that the replacement fluid may more accurately reflect the electrolyte losses. Otherwise, a solution of 0.45 % NaCl can be used initially and altered as the clinical situation continues to develop and further electrolyte determinations are made.

If the child's volume status or the adequacy of renal function is difficult to discern initially, it is best to provide the child with replacement of both insensible and ongoing losses. This approach should maintain the child's current volume status and allow for further determination of the appropriateness of more vigorous hydration or conversely fluid restriction as the clinical situation clarifies. Monitoring the child's weight on at least a daily basis and documenting the child's total fluid intake and output will also assist in arriving at a proper hydration regimen.

Assessing the child's current electrolyte status and monitoring the loss of electrolytes in the urine or in any other source of significant output will help tailor the daily electrolyte prescription. An

understanding of the pathophysiology underlying the child's renal dysfunction will also be useful. The child who has profound tubular electrolyte losses will require more sodium on a daily basis than the child who is edematous and total body salt overloaded from his nephrotic syndrome. The child with chronic renal insufficiency and hypertension mediated by long-standing salt and water overload may actually benefit from diuretic therapy to remove salt and water rather than any further volume expansion with saline.

Certainly the provision of supplemental potassium to the child with renal dysfunction must be done judiciously. The oliguric or anuric child should receive no potassium until it is well documented that serum potassium levels are low or that there are extrarenal potassium losses (for instance losses from diarrheal stool). The child with marginal renal function should receive small amounts of potassium (approximately 1 mEq/kg/day) with at least daily assessment of electrolyte balance to determine adequacy and appropriateness of continued potassium supplementation.

Fluid and Electrolyte Therapy in the Pediatric Intensive Care Unit

Critically ill children present a challenge to the clinician attempting to prescribe appropriate fluid and electrolyte therapy. Oftentimes, there may be acute kidney injury or multiorgan failure complicating management decisions. With such children, rote reliance on standard equations or practice guidelines to prescribe fluid and electrolyte therapy may create significant fluid and electrolyte anomalies. Rather than prescribing set maintenance requirement of fluid or electrolytes, the clinician should assess the patient's individual fluid and electrolyte needs in the context of the underlying pathophysiology, the current volume status, the efficacy of tissue perfusion, the current ventilatory requirements, and the current renal function. Whenever there is concern about incipient or exacerbating fluid overload, it is important to review the volume and type of fluids being provided. Maximizing the concentration of

continuous medication drips and assessing medication compatibility for simultaneous infusions are important steps in limiting total daily fluid input. Initially, it is crucial in these critically ill children to ascertain that their intravascular space is replete to help maintain hemodynamic stability. Once a patient is felt to be intravascularly replete, maintaining euvolemia by providing insensible water losses as well as replacing any ongoing fluid and electrolyte losses should maintain fluid and electrolyte balance.

Oftentimes, despite a desire to limit fluids in the critically ill child, medication requirements, nutritional needs, and hemodynamic insufficiency may result in very large daily fluid loads. There may also be situations in which increased vascular permeability causes a critically ill child to become massively volume overloaded but with a decreased effective circulating volume. In other words, renal and tissue perfusion may be sluggish because fluid has moved from the intravascular space into the interstitial space. In this setting, there may be a need to continue to administer large volumes of fluid to maintain circulatory integrity with the knowledge that such infusions will only exacerbate the total body fluid overload. Aggressive diuretic therapy may prove useful especially if renal function is not compromised. Combination diuretic therapy utilizing agents that work at separate sites along the renal tubule may be necessary. Ultimately, the use of either periodic or continuous ultrafiltration may be beneficial to these patients by allowing ongoing fluid administration but limiting the daily imbalance between fluid intake and output. Ultrafiltration may be accomplished via peritoneal dialysis, by intermittent hemodialysis with ultrafiltration or by utilizing one of the slow continuous ultrafiltration techniques now known as continuous renal replacement therapy (CRRT)). The recognition that volume overload has a deleterious effect on many aspects of patient management and seems to be a strong prognostic indicator of poor ultimate outcome suggests that early ultrafiltration should be considered in critically ill patients [152].

If ultrafiltration is initiated, extreme vigilance is necessary to prevent exacerbation of intravascular depletion and the development of prerenal azotemia or frank renal failure. Special care must be taken with the continuous modalities to insure that ultrafiltration rates are periodically reassessed and readjusted. Furthermore, because the electrolyte losses that accompany the ultrafiltration of fluid are isotonic, the electrolyte content of infused fluids must be adjusted to match the composition of the ultrafiltrate, especially if there is no component of dialysis ongoing that may blunt the development of serum electrolyte anomalies. As a result, serum electrolyte values need to be followed in a serial fashion with periodic review and readjustment of the composition of supplemental intravenous fluids.

Abnormalities in Serum Sodium Complicated by Kidney Injury

Because of the important contribution of serum sodium to serum osmolality, alterations in serum sodium, especially coupled with alterations in BUN related to renal failure, can complicate the usual approach to a child with fluid and electrolyte anomalies. Generally, there are greater concerns with hypernatremia and renal failure since the need to correct the sodium in a slow fashion can be problematic when renal replacement therapy needs to be initiated for clearance of urea. Balancing the correction of sodium and the hyperosmolar state with the clearance of urea requires a carefully considered plan that is grounded in a firm understanding of fluid and electrolyte homeostasis.

In most cases of hypernatremia related to severe dehydration, some degree of acute kidney injury is present. This renal dysfunction is usually "prerenal" in nature, a result of a decreased effective circulating volume rather than an intrinsic glomerular or tubular disorder. Most often, in the course of rapid restoration of perfusion and early rehydration, urine output increases and azotemia begins to resolve.

Alternatively, there are occasional cases in which due to intrinsic renal dysfunction or acute tubular necrosis, the renal insufficiency will not respond to volume infusion, and, in fact, the provision of excess volume may contribute to

significant volume overload. In these cases, there may be need to consider some form of renal replacement therapy to assist in the controlled correction of fluid and electrolyte derangements, especially if the renal failure is oliguric or anuric in nature. Such an example is detailed in the following case study:

A 15-year-old boy presents with several weeks of polyuria, severe weight loss, fatigue, and poor oral intake. He is diagnosed as having diabetes mellitus with ketoacidosis by his pediatrician and referred to an emergency department for management. At this point, his serum sodium is 154 mEq/L, his creatinine is 3.0 mg/dl, and his BUN is 30 mg/dl. In the emergency department, the child receives several bolus infusions of normal saline supplemented with sodium bicarbonate and is started on an insulin drip. He is admitted and continues to receive brisk intravenous hydration with normal saline with bicarbonate supplementation per a practice guideline for treating children with diabetic ketoacidosis. He is noted to be oliguric and this does not improve with several more hours of hydration with normal saline following the guideline hydration recommendations. The next morning, laboratory values reveal a serum sodium of 165 mEq/L, a creatinine of 4.5 mg/dl, and a BUN of 50 mg/dl. He has made only 75 ml of urine in the last 8 h and is developing some mild peripheral edema.

In this case, the renal insufficiency and poor urine output have complicated the usual management of diabetic ketoacidosis and has exacerbated an underlying hypernatremia. Given the patient's evolving renal failure, it is not feasible to provide the necessary volume of free water to correct the hypernatremia without contributing to further volume overload. Because of the apparent progressive renal failure, it would also be useful to correct the hypernatremia in case dialysis becomes necessary for urea clearance. By performing controlled ultrafiltration on the patient and replacing back the volume ultrafiltered with free water, the serum sodium could be corrected without exacerbating the volume status.

With a serum sodium of 165 mEq/L and an estimated TBW of 42 L (70 kg × 0.6 L/kg), this boy has free water needs of 7.5 L to lower his serum sodium to the 140 mEq/L range ([165/140 × 42] − 42). Since the patient is now significantly hypernatremic and has been subject to various fluid and electrolyte shifts as his diabetic ketoacidosis has been treated, it would be prudent to correct his serum sodium by no more than 10–12 mEq/day over the course of 3 days. Thus, if the boy undergoes ultrafiltration with a goal of 2.5 l removed daily, and the ultrafiltration volume each day is replaced back totally as free water, the serum sodium should be in the normal range in 3 days time. The ultrafiltration goal could be achieved over the course of a few hours each day if the patient were hemodynamically stable or over a more prolonged period of time each day if there were concerns regarding hypotension. Thus, either a conventional hemodialysis setup could be used for relatively rapid ultrafiltration only or a continuous filtration circuit for either rapid or slow filtration.

Since the fluid removed in ultrafiltration is isonatremic to the serum sodium, the sodium concentration of each liter of ultrafiltrate should mirror the serum sodium concentration at the time of ultrafiltration. Thus, on the initial day of ultrafiltration, each liter of ultrafiltrate would contain a sodium content of 165 mEq/L. By providing back the volume ultrafiltered each day as free water, the serum sodium content could be expected to fall, in this case, by about 8–10 mEq/L/day.

It is important to recognize that free water must be provided back to the patient to make up for the ultrafiltration losses. Otherwise, since the ultrafiltrate is isotonic, there will be no change in the serum sodium concentration, and the ultrafiltration may potentially exacerbate the renal failure by depleting the intravascular space and the effective circulating volume.

Moreover, it is also important to recognize that the boy's overall daily fluid needs will be greater than the daily ultrafiltration volume alone since maintenance fluid requirements and any ongoing fluid losses must also be considered. Since the boy is in renal failure, his maintenance fluid needs can be scaled back to insensible losses of 300 ml/m^2/day and, in this case, there are no ongoing losses. Thus, each day for the next 3 days, this 70-kg

patient needs to receive approximately 500 ml/day of insensible losses and 2,500 ml/day of ultrafiltration replacement or a total of 3,000 ml/day. His maintenance sodium requirements are 3 mEq/kg/ day. Although it may seem counterintuitive to provide a hypernatremic patient with maintenance sodium, disregarding these requirements will result in a more rapid correction of the hypernatremia than desired. If the child were to receive a saline infusion of 0.45 % NaCl at a rate of 125 ml/h, this will provide just over 3 mEq/kg/ day of sodium in a total volume of 3 L/day.

If the child with hypernatremia has profound renal failure and requires dialysis for urea clearance, the dialysis prescription must take into account the need to correct the serum sodium slowly. Normally, regardless of the modality of renal replacement therapy, most dialysate contains sodium isotonic to the normal serum sodium range. It may prove detrimental, however, to dialyze a patient who is very hypernatremic against a dialysate with a sodium concentration that is 30 mEq/L lower than the patient's serum sodium concentration. The diffusional gradient during dialysis would lead to more rapid correction of the serum sodium than the desired drop of approximately 1 mEq every 2 h.

Although most hemodialysis machines can be readjusted so that the dialysate produced will have a sodium content as high as the low to mid-150s, this still may not reduce the gradient sufficiently in cases of severe hypernatremia. In those situations, by maximizing the sodium concentration of the dialysate and by performing dialysis for limited amounts of time, one could minimize the drop in serum sodium. Still, there would need to be frequent assessments of the serum sodium concentration, and overall clearance may need to be sacrificed to prevent too rapid correction of the serum sodium and a rapid concomitant decrease in the serum urea that may increase the chances for dialysis disequilibrium.

Alternatively, a continuous hemodiafiltration technique such as continuous venovenous hemodiafiltration (CVVHDF) could be performed. By asking the hospital pharmacy to increase the sodium content of the dialysate and replacement fluid to within 10–12 mEq/L of the serum sodium concentration, the diffusional gradient for sodium clearance could be minimized. Then, by making appropriate adjustments in the sodium content of the dialysate as the serum sodium falls, the serum sodium levels could be reduced gradually by 10–12 mEq/L/day, while at the same time adequate urea clearance and ultrafiltration for most situations would be achieved.

Peritoneal dialysis has also been used in cases of severe hypernatremia [153–155]. Again, the concentration of sodium in the dialysate may need to be adjusted upwards in severe hypernatremia to prevent too rapid clearance of sodium. In addition, since the degree of clearance and ultrafiltration may not be as precisely controlled as with hemodialysis or hemodiafiltration, frequent assessment of electrolyte values will be necessary. Manipulation of dwell volumes and dwell times will also influence overall clearance and the use of smaller dwell volumes for longer periods of time will help to minimize sodium clearance.

In contradistinction to hypernatremia, since hyperosmolality is less common with hyponatremia, in some ways it is easier to employ renal replacement therapy in the setting of severe hyponatremia and concomitant renal insufficiency. Again, the focus needs to be on the rapidity of the correction of the serum sodium. In conditions of severe but asymptomatic hyponatremia of some chronicity, the rate of correction of serum sodium should parallel the rate of correction recommended in hypernatremia – approximately 10–12 mEq/L/day. Correction of chronic hyponatremia at a more rapid rate has been associated with the development of central pontine myelinolysis.

All of the manipulations described above for hypernatremia and renal failure can be utilized with hyponatremia and renal failure, with the understanding that the dialysate sodium concentration should now not exceed the serum sodium value by 10–12 mEq/L. Conventional hemodialysis machines can be adjusted to produce dialysate with a sodium concentration as low as the mid-120s. In the very rare situation in which a child with profound hyponatremia (<110 mEq/L) was being hemodialyzed, brief hemodialysis runs

may be necessary initially to prevent too rapid correction of the serum sodium level and the attendant risk of central pontine myelinolysis. If dialysate is being custom prepared for peritoneal dialysis or hemodiafiltration, precise alterations in the electrolyte content can be made more readily to reduce the sodium gradient.

The local resources, the training of ancillary staff, the unique circumstances of each patient, and the comfort of the clinician with different modalities of renal replacement therapy will guide the choice of therapy when faced with renal failure and significant serum sodium anomalies. The actual modality of renal replacement therapy utilized is less important than careful attention to the rate of correction of the electrolyte anomaly, to the rate of urea clearance being achieved, and to the clinical response of the patient to ongoing therapy.

Potassium

There are several homeostatic mechanisms in place to maintain the usual high concentration of potassium in the intracellular space. These rely on the sodium–potassium ATPase found on the cell membrane, the effects of insulin and adrenergic hormones on transcellular potassium movement, and the effects of nephron mass, GFR, hydration, urinary flow, and especially aldosterone on renal potassium excretion and net body potassium balance.

In normal circumstances, potassium distribution is extremely well regulated since the gradient between the intracellular and extracellular spaces plays a crucial role in the process of nerve excitation and myocyte contraction. This explains why nearly 99 % of total body potassium can be found intracellularly and why aberrations in potassium handling that disrupts the usual gradient can be not only detrimental to growth and development but also life threatening if cardiac conduction and contractility or respiratory muscle function is significantly affected. The intracellular localization of most body potassium stores also explains why serum potassium levels are not a good estimate of total body potassium stores, and the clinician

needs to consider the possibility of transcellular redistribution when interpreting any aberrant serum potassium level before making decisions to supplement or restrict its provision.

In children, abnormalities in potassium homeostasis are uncommon but, as seen with other electrolytes like sodium, physiologic perturbations that may occur with acute illness or certain chronic medical conditions can interfere with normal regulatory processes and lead to clinically significant imbalances in potassium. As with other electrolyte issues, the ramifications of any abnormality generally reflects on how quickly it has evolved, how extreme it has become, and whether other medical conditions are more likely to be adversely affected or even perpetuate the abnormality.

Hyperkalemia

Hyperkalemia is usually defined as a serum potassium concentration exceeding 5.5 mEq/L. In most children, intact homeostatic mechanisms keep serum potassium levels less than 5 mEq/L. With infants, there can be a higher range of normal potassium values because of baseline reduced GFR and some insensitivity to aldosterone, with levels as high as 6 mEq/L not uncommon. There is generally little clinical consequence to serum potassium values up to 6 mEq/L, and most children rarely manifest any significant symptoms related to hyperkalemia until serum potassium levels exceed 7 mEq/L. At that level, there may be lethargy and discernible muscle weakness or even paralysis, often initially affecting the legs. There can also be sporadic heart palpitations or arrhythmias that can progress to asystole. As with any electrolyte aberration, high serum potassium levels should be considered in the clinical context of the child's current medical status, and significantly elevated levels require urgent assessment and management tailored to take into account any comorbid conditions.

Causes of Hyperkalemia in Children

The causes of hyperkalemia in children can be grouped into several broad categories based on

Table 11 Causes of hyperkalemia in children

Category	Cause
Pseudohyperkalemia	Technical issue with phlebotomy
	Hemolysis of specimen in handling
	Release of potassium from leukocytes or platelets in blood sample
Increased potassium intake	IV fluids, peripheral nutrition, or potassium-containing medications
	Potassium-based table salt substitutes
Transcellular potassium redistribution	Conditions with loss of cell membrane integrity
	Rhabdomyolysis
	Tumor lysis
	Hemolytic states
	Acidosis
	Periodic paralysis
Decreased potassium excretion	Reduced GFR
	Decreased effective circulating volume
	Impaired tubular secretion
	Reflux nephropathy
	Obstructive uropathy
	Type IV renal tubular acidosis
	Sickle cell nephropathy
	Impaired renin–angiotensin–aldosterone axis
	Congenital adrenal hyperplasia
	Pseudohypoaldosteronism
	Drug effect (ACE/ARB, eplerenone, spironolactone, aliskiren)

underlying pathophysiology (Table 11). In children, hyperkalemia may often be spurious and related to technical issues commonly seen with pediatric phlebotomy. Such pseudohyperkalemia needs to be distinguished from true hyperkalemia that usually arises related to a disturbance in the renal excretion of potassium or movement of normally sequestered intracellular potassium into the extracellular space. Hyperkalemia in children is rarely due to excess potassium ingestion alone and sustained high potassium levels usually point towards some impairment in renal potassium excretion.

Pseudohyperkalemia

In pseudohyperkalemia, the elevated potassium level does not reflect the child's true potassium balance. Especially in small children, there can be hemolysis of a blood sample due to technical reasons, with release of erythrocyte potassium stores [156, 157]. Smaller gauge needles must often be used or samples withdrawn through indwelling small gauge intravenous catheters, with the need to apply significant suction to the attached syringe to obtain necessary sample volume. These techniques are up to sixfold more likely to result in a hemolyzed sample than with the use of vacuum flow devices [156].

Children are also often less cooperative with the phlebotomy procedure and may require physical restraint or may repetitively contract muscles in an extremity while undergoing phlebotomy, leading to local potassium release from myocytes and a hyperkalemic blood sample not reflective of true systemic potassium levels. Additionally, hyperventilation seen with intense crying can mediate a very acute respiratory alkalosis with potassium shifting out of cells and a rapid increase in serum potassium by as much as 1 mEq/L [156, 158].

In children with marked leukocytosis or thrombocytosis such as seen with leukemias or myeloproliferative disorders, there may also be potassium egress from white cells or platelets as the blood sample clots. A plasma potassium assay decreases the chances of such a confounding result.

In most cases of pediatric pseudohyperkalemia, an elevation in serum potassium levels is unexpected on clinical grounds, and details of the phlebotomy procedure or laboratory confirmation of hemolysis in the sample allow the result to be put into proper perspective. It does become more difficult in children with preexisting alterations in homeostatic mechanisms due to acute illness or chronic disease to disregard high potassium levels, and although there can always be an element of pseudohyperkalemia, it is judicious to repeat another sample to determine that a

normal level exists before attributing high levels to pseudohyperkalemia exclusively.

Increased Potassium Intake

In normal children, even very large dietary potassium loads are unlikely to result in sustained hyperkalemia. Homeostatic mechanisms that promote potassium influx into cells and aldosterone-mediated enhanced kaliuresis tend to prevent hyperkalemia from intake of most foods. In small children with smaller volumes of distribution, exposure to some nutritional supplements such as salt substitutes that can contain up to 80 mEq potassium chloride/teaspoon can result in potassium loading that exceeds by many fold normal dietary potassium intake and can overwhelm homeostatic mechanisms [159].

Children with impaired GFR may, however, require dietary potassium restriction, though gut excretion of potassium increases with chronic renal dysfunction as a compensatory mechanism, even in the setting of children maintained chronically normokalemic on dialysis [160].

In hospitalized children, iatrogenic errors in the concentration of potassium in intravenous fluids, peripheral nutrition, or certain intravenous medications can result in the inadvertent provision of large potassium loads, and hospitalized children receiving potassium supplementation either orally or in some intravenous form need to be monitored for the development of hyperkalemia.

Transcellular Redistribution of Potassium

Breakdown of normal tissue or rapid cell lysis can result in the release of large amounts of intracellular potassium along with other intracellular electrolytes into the extracellular space and plasma water. This often occurs in the setting of rhabdomyolysis from crush injury sustained in accidents or natural disasters or after periods of extreme exercise, in tumor lysis syndrome in leukemia or lymphoma, or with severe hemolytic processes. There may often be accompanying acute kidney injury that exacerbates the hyperkalemia and complicates its management.

Transcellular redistribution may also occur in the absence of cellular damage. In metabolic acidosis, the movement of hydrogen intracellularly causes extracellular potassium shift to maintain electroneutrality. In children, metabolic acidosis is often mediated by decreased effective circulating volume from either severe dehydration or infection. This volume imbalance may exacerbate the hyperkalemia by reducing GFR and reducing renal potassium excretion. The restoration of adequate intravascular volume and tissue perfusion generally corrects the acidosis and hyperkalemia. A similar transcellular shift can be seen with insulin deficiency and diabetic ketoacidosis, though the hyperkalemia can sometimes be blunted early in this process by urinary potassium losses from an osmotic diuresis and excreted keto acids.

In hyperkalemic periodic paralysis, hyperkalemia is also related to transcellular relocation of potassium. This is an autosomal dominant condition in which a voltage-gated sodium channel near the neuromuscular junction is affected and allows for ongoing movement of potassium ions from the muscle into the bloodstream in response to stimuli that usually reduce potassium flux [161]. Hyperkalemic periodic paralysis may present as early as infancy and need to be considered in any child with hyperkalemia and muscle weakness.

Abnormalities in Renal Excretion

Intrinsic or Acquired Glomerular or Tubular Dysfunction

Intrinsic anomalies in the renal handling and excretion of potassium or acquired conditions impairing normal excretion are a common cause of significant pediatric hyperkalemia. Although aldosterone effect on the distal nephron is a key to potassium homeostasis, any renal disease that impairs effective glomerular filtration will limit absolute potassium clearance. As GFR falls in a child with chronic kidney disease, the ability to excrete potassium tends to stay relatively well compensated, especially when the GFR exceeds 30 ml/min/1.73 m^2. With more profound functional impairment, especially in the setting of lower urine output, hyperkalemia may be more commonly encountered.

With children with obstructive uropathy or reflux nephropathy, there is often a distal tubular

resistance to aldosterone that results in a type IV renal tubular acidosis (RTA) and associated hyperkalemia, even when the GFR is well preserved. In infants, there can also be immature tubular responsiveness to aldosterone that is developmental during early life, and this helps to explain why babies have a tendency towards higher baseline serum potassium levels than older children. In children with sickle-cell disease who have impaired medullary blood flow and ensuing hypoxic renal tubular injury, there is also a tendency towards impaired aldosterone sensitivity over time.

One study of children with acute febrile urinary tract infection but no concomitant urinary tract obstruction or chronic kidney disease demonstrated significantly increased rates of hyperkalemia compared to children with other febrile illnesses [162]. This would suggest that, even in structurally normal distal renal tubules, conditions with interstitial inflammation such as seen with pyelonephritis can impact normal potassium handling.

Certain drugs, most notably potassium-sparing diuretics, can similarly impact normal tubular renal excretion of potassium. These medications are often used for disease states such as heart or liver failure in which effective circulating volume is also impaired and GFR may be suboptimal, further exacerbating potential kaliuresis.

Decreased Effective Circulating Volume

A much more common reason to see hyperkalemia in children is a state of low effective circulating volume that results in either ineffective tissue perfusion and the generation of a metabolic acidosis or sodium and water avidity in the proximal portion of the nephron. As a result, there is decreased distal flow of filtrate in the nephron and a decreased concentration of sodium in any filtrate actually presented to the distal nephron. This leads to what is often termed a functional renal tubular acidosis or impaired aldosterone-mediated kaliuresis and acid excretion that is not related to any inherent anomaly in the channels or receptors in the distal nephron. Especially in young children, there is an increased tendency to develop significant dehydration and hemodynamic instability with acute illness, and it is not uncommon to

see significant hyperkalemia related to effective volume depletion alone and the effects described above [163].

In some children with chronically marginal hydration and a diet that is low in sodium content, this same situation of low distal delivery of sodium exists and can result in high potassium levels. This is most often seen in babies with feeding difficulties since both breast milk and formula contain little sodium.

Decreased Activity of Renin–Angiotensin–Aldosterone System

Although infrequently encountered, endocrine anomalies impacting the RAAS can result in infants or young children presenting with hyperkalemia. Congenital adrenal hyperplasia (CAH), and especially its most common form 21-hydroxylase deficiency, results in impaired mineralocorticoid production, salt wasting, and hyperkalemia. CAH is part of the newborn screen across the entire United States and is included in newborn screening in many foreign countries, leading to its identification prior to significant electrolyte anomalies in many infants. Primary adrenal insufficiency is a rarer condition than CAH and affected children may present with hyperkalemia, though hyponatremia and hypotension are more common [164].

Pseudohypoaldosteronism, an abnormality of mineralocorticoid receptor activity, is an even rarer endocrine condition. Children present characteristically with hyponatremia, hyperkalemia, and metabolic acidosis, but serum aldosterone levels are elevated, underscoring that the issue is in the cell receptor and not in mineralocorticoid production. An autosomal dominant form only affects the kidney and, over time, affected children may show spontaneous improvement due to maturational enhancement of tubular sodium transport. In the autosomal recessive form, there is generally pronounced distal tubular epithelial sodium channel dysfunction that presents early in childhood and requires significant ongoing sodium supplementation [165].

Children being treated with spironolactone, eplerenone, aliskiren, or one of the angiotensin-converting enzyme inhibitors or angiotensin

receptor blockers will also have decreased miner-alocorticoid production or activity and may develop hyperkalemia directly related to their use. Many of these drugs are used in children with medical conditions that already predispose to hyperkalemia due to adverse affects on effective volume, GFR, and baseline renal tubular handling of solute.

Evaluation of Hyperkalemia in Children

In many children, the clinical presentation or known preexisting medical conditions will point clearly to the underlying etiology of the hyperkalemia and its proper treatment, and there is little need for an extensive diagnostic evaluation. For instance, children with tumor lysis, rhabdomyolysis, structural or functional kidney disease, or markedly decreased effective circulating volume all are likely to have correction in their potassium imbalance as the underlying condition is treated. In children with no obvious reason for hyperkalemia and normal renal function and volume status, a high index of suspicion for pseudohyperkalemia must exist and potassium values should be confirmed prior to any further evaluation.

In some children, however, the cause of a persistently high potassium level will not be obvious, and it is important to assess the renal handling of sodium and potassium as well as the renin–angiotensin–aldosterone system carefully. The direction of any further evaluation is then guided both by the medical history and initial results from typical screening laboratories of blood and urine (Table 12).

In most children, hyperkalemia should result in a random urinary potassium level that exceeds 20 mEq/L and often exceeds 40 mEq/L. Very high random urinary potassium values (>80 to 100 mEq/L) almost always point towards intact mechanisms to achieve kaliuresis, and diagnostic focus should shift to an issue with potassium intake or cellular release rather than renal excretion.

Since random urinary potassium levels may be affected by the degree of urinary concentration and by the ability of the distal tubule to secrete

Table 12 Diagnostic studies to assess unexplained hyperkalemia in children

Laboratory test	Key findings
Complete blood count, platelet count	Hemolysis, thrombotic microangiopathy, blood dyscrasias
Creatinine	Reduced GFR
Electrolytes	Metabolic acidosis or other electrolyte aberration
Urine electrolytes and urine creatinine (best done concomitantly with serum electrolytes and creatinine)	Evidence of inappropriate urinary K excretion ($U_K < 20$ mEq/L in setting of hyperkalemia)
	Evidence of reduced effective volume or reduced distal tubule sodium delivery ($U_{Na} < 20$ mEq/L)
Lactic dehydrogenase	Elevated levels suggesting hemolysis
Creatine kinase	Elevated levels suggesting muscle injury
Serum aldosterone and plasma renin activity	Aberrant levels suggest endocrine abnormality

potassium in conjunction with reabsorption of sodium, it is often necessary to also measure urinary sodium and urinary osmolality to more completely assess the appropriateness of random urine potassium results. Low random urinary sodium values (<20 mEq/L) demonstrate that there is renal sodium avidity, and this may limit the potential secretion of potassium in the distal nephron even in the face of a normal hormonal milieu and normal renal tubular cell receptors and channels. Measures that improve the effective volume and provide more sodium for distal tubular delivery augment kaliuresis.

For some time there was interest in calculation of the transtubular potassium gradient (TTKG) to help determine if there was appropriate mineralocorticoid effect in states of hyperkalemia in pediatric patients [166]. The TTKG estimated the ratio of the potassium concentration at the end of the cortical collecting tubule, the site responsible for most of potassium secretion, to blood potassium levels. The TTKG was predicated on the assumption that changes in the osmolality in the collecting duct were only due to water

reabsorption, but there is now evidence of urea cycling in the collecting duct that invalidates this premise [167]. Accordingly, the TTKG is no longer considered a reliable assessment of mineralocorticoid effect and, when there is clinical suspicion of an endocrine issue interfering with potassium handling, serum aldosterone and plasma renin activity should be measured.

Treatment of Hyperkalemia in Children

The degree of potassium elevation and its likelihood to cause immediate cardiac arrhythmias guide the urgency of treatment and the therapies employed. Specific interventions range from limiting further potassium intake, to facilitating intracellular shifts of potassium from the extracellular space, to augmenting potassium excretion in the urine or stool, to actually removing potassium from the extracellular space by dialysis. Outside of the significant clinical evidence that exists to demonstrate that dialysis is an effective way to correct hyperkalemia and prevent life-threatening complications, there have been few pediatric-specific studies that have addressed the overall efficacy of some of these maneuvers, although all of them are commonly employed in clinical practice [168] (Table 13).

General Approach to Therapy

In children with potassium levels >6.5 mEq/L or specific immediate clinical concern for cardiac effects of hyperkalemia prior to the laboratory value having returned, an electrocardiogram should be obtained to look for abnormal atrial (P wave) or ventricular (QRS complex) depolarization or abnormal repolarization (T wave). In children, ECG changes are more likely to be related to serum potassium levels than in adults, who are more prone to preexisting cardiac conduction abnormalities or cardiovascular disease. As hyperkalemia develops, initial ECG findings include tall, peaked, symmetric T waves and shortened QT intervals. With more severe hyperkalemia, P waves become flattened, PR intervals prolonged, and QRS complexes widened. Eventually, as a harbinger to ventricular

Table 13 Treatment of hyperkalemia in children

Potassium level <6 mEq/L	Limit potassium intake Optimize effective volume
Potassium levels 6–7 mEq/L No ECG changes or only peaked T waves If other ECG changes, consider therapy for K > 7 mEq/L	Stop potassium intake Optimize effective volume Consider loop diuretic therapy such as furosemide 1 mg/kg q 6 h Consider sodium polystyrene sulfonate 1 g/kg up to 40 g q 4 h given po, pg, or pr
Potassium levels >7 mEq/L	Stop potassium intake Optimize effective volume Nebulized beta agonist such as albuterol Calcium gluconate (10 %): 10 mg/kg IV to stabilize myocardium Insulin and glucose: 0.1–0.3 units/kg regular insulin and 2–4 ml/kg D25 Consider sodium bicarbonate (only after calcium provision) 1 mEq/kg Sodium polystyrene sulfonate 1 g/kg up to 40 g q 4 h given po, pg, or pr Consider loop diuretic therapy such as furosemide 1 mg/kg IV q 6 h Urgent dialysis if no improvement or concomitant significant renal failure

fibrillation, there may come to be a sinusoidal pattern as the QRS complex merges with the T wave. Not all children with hyperkalemia will manifest ECG changes and absence of ECG change does not preclude the need for potential therapy for significant potassium elevation.

In children with no ECG changes or peaked T waves alone and more moderate levels of hyperkalemia (<7 mEq/L), initial therapy includes limiting further potassium intake and promoting potassium loss in the stool with an enteral cation exchange resin, with consideration of augmenting urinary potassium losses with the use of a loop diuretic.

In children with ECG changes other than peaked T waves or with more pronounced

hyperkalemia (>7 mEq/L), calcium infusion is used to stabilize the cardiac membrane excitability that comes with hyperkalemia. Although its protective effects begin quickly, its duration may be short-lived and further infusions may be necessary. Concomitantly, therapies that promote the shift of potassium into the intracellular space such as nebulized beta agonists or intravenous insulin and glucose are begun and enteral cation exchange resin given.

In children unresponsive to such maneuvers or with concomitant severe renal dysfunction, dialysis may be necessary. Generally, hemodialysis is the preferred modality to reduce potassium levels most quickly and in the most controlled fashion. In some centers, local resources may make forms of CRRT a better option than conventional hemodialysis. Although peritoneal dialysis can be used, potassium loss will be less efficient and less well controlled.

Therapies Redistributing Potassium

These therapies are rapid in onset but generally have limited duration since no net potassium is removed from the child and, as the therapeutic effect of intervention wanes, potassium can redistribute back to the extracellular space. As a result, most of these therapies are done along with other maneuvers to either remove potassium from the body or to adequately reverse whatever is causing the hyperkalemia to develop. By themselves, they are less effective in providing a management solution.

Since securing intravenous access in young children can be more problematic than with adolescents or adults, using inhaled beta agonists can be an attractive initial option to move potassium intracellularly. This maneuver should be avoided in children manifesting any preexisting cardiac arrhythmia and children should be on a cardiac monitor during its provision. Tachycardia and tremors are common, but are usually short-lived. Reductions of serum potassium concentrations by 1.5 mEq/L have been obtained as quickly as within an hour [169]. Such therapy has been shown to be safe and effective even in premature infants, with no differences in heart rate, CNS symptoms, ECG anomalies, hyperglycemia, or

intraventricular hemorrhage when two nebulizations with albuterol were compared to two saline nebulization treatments [170].

With intravenous access, other temporizing maneuvers such as infusion of insulin and glucose or systemic alkalinization with sodium bicarbonate can be attempted. Rates of these infusions must be calculated on a case-by-case basis according to the child's weight, given the broad spectrum of body sizes in pediatric patients. If insulin is provided, glucose should be given concomitantly to prevent hypoglycemia, and the potassium level should start to fall within 15 min of insulin provision with peak insulin effect by an hour. When sodium bicarbonate is infused repetitively, the risk of developing hypernatremia exists.

There has been limited experience with a solution containing fixed concentrations of calcium gluconate, insulin, dextrose, and sodium acetate in treating hyperkalemic children [171]. An advantage to such a solution is that it could be readily prepared by hospital pharmacies to be available in hyperkalemic emergencies and could then be infused continuously to allow for more sustained effect, although the caustic properties of such a solution may prevent its provision through peripheral vasculature.

Therapies Removing Potassium from the Body

Diuretics – Although loop and thiazide diuretics can promote kaliuresis, given that a large proportion of children with hyperkalemia will have decreased effective circulating volume or renal dysfunction, the effectiveness of diuretic therapy in most hyperkalemic children is limited, especially in the urgent setting. In children with adequate effective volume, using these diuretics and maintaining a diuresis with ongoing optimization of effective volume could be considered as an adjunct. Such therapy can especially be considered in children with persistently high but clinically less urgent hyperkalemia (5.5–6.5 mEq/L).

Enteral cation exchange resins – Polystyrene sulfonates have been used for decades in children with hyperkalemia. Dissolved in water and taken orally or given as a retention enema, they work by exchanging a counterion such as sodium or calcium for potassium across the large intestine.

The potassium polystyrene sulfonate complex that results cannot be digested and gets excreted in stool, thereby effectively removing potassium from the body. Each gram of resin may bind as much as 1 mEq of potassium. During this process, the resin releases an equivalent amount of its counterion, and provision of large amounts of these resins can lead to sodium or calcium imbalances.

To prevent constipation or fecal impaction, polystyrene sulfonates were mixed for many years with sorbitol that would serve as an osmotic laxative. Reports of colonic necrosis and perforation in patients receiving such mixtures, especially in postsurgical settings where there was impaired gastrointestinal mobility, prompted the FDA to warn that sodium polystyrene sulfonate should not be administered concomitant with sorbitol [172]. To counteract its constipating effects, polystyrene powder or powder mixed with water can be given with lactulose or polyethylene glycol 3,350 preparations as laxatives.

Although widely used in children with hyperkalemia both acutely and chronically, one comprehensive review found no randomized evidence for the efficacy of these binders in the emergency situation [173], and most of the limited studies of its efficacy have been in individuals with chronic kidney disease or after multiple doses [173, 174]. Although the only therapy short of dialysis that can remove potassium from the body, in most hyperkalemic children, however, its provision in the setting of significant hyperkalemia is still regarded as a reasonable therapy by most pediatric clinicians.

Hypokalemia

Hypokalemia is usually defined as a serum potassium level less than 3.5 mEq/L, although, in most children and adolescents, levels between 3 and 3.5 mEq/L are asymptomatic, and some reference laboratories even set the lower limit of normal in this range. There may also be measurement differences between samples processed by conventional laboratory AutoAnalyzers and samples assayed by point-of-care blood gas analyzers that are often used in critical care areas for rapid turnaround of results. One study of 60 children demonstrated that samples done by blood gas analyzers averaged nearly 0.5 mEq/L lower than conventional assays [175].

Clinically, hypokalemia is encountered more commonly than hyperkalemia, especially in hospitalized children. In studies of children in pediatric intensive care unit, up to 20 % had hypokalemia on admission and up to 40 % ultimately had hypokalemia identified during the course of their ICU stays [176–178]. Hypokalemia was more likely seen in children with cardiac or renal disease or with hemodynamic collapse, as well as in children with infections or who required calcium supplementation [176].

Children are often asymptomatic until serum potassium levels approach 2.5 mEq/L. Since low extracellular potassium levels alter the usual transcellular potassium gradient, significant clinical manifestations of hypokalemia often relate to changes in muscle contraction or cardiac conduction [179]. Muscle weakness develops starting in the legs and then may ascend. With profound hypokalemia, respiratory muscles can become involved and there may even be rhabdomyolysis. Smooth muscle dysfunction in the gastrointestinal tract can present as nausea, constipation, or frank ileus. In terms of cardiac effects, children with hypokalemia often manifest characteristic ECG changes with PR interval prolongation, dampening of the T waves, and ST depression. As hypokalemia exacerbates, there can be the appearance of U waves as well [179, 180].

With chronic hypokalemia there can also be direct renal effects leading to polyuria. This polyuria arises related to several mechanisms, including the stimulating effect of hypokalemia on thirst and other neuroendocrine factors as well as the impact of persistent hypokalemia on aquaporin protein depletion in the cortical collecting duct limiting the number of effective water channels [48, 181, 182].

Causes of Hypokalemia in Children

The causes of hypokalemia in children can be grouped into four broad categories based on underlying pathophysiology: decreased

Table 14 Causes of hypokalemia in children

Decreased potassium intake
Chronic dietary restriction
Malnutrition, eating disorders
Iatrogenic errors in nutritional supplementation
Transcellular redistribution of potassium
Alkalosis
Endocrine effects
Insulin, catecholamines, thyroid hormone
Periodic paralysis
Medications
Beta-adrenergics, chloroquine, antipsychotic agents
Extrarenal potassium losses (usually GI tract)
Diarrhea
Vomiting
Nasogastric tube losses
Renal potassium losses
Increased delivery of sodium and water to distal tubule
Diuretics, mannitol, keto acids
Renal tubular acidosis
Hyperaldosteronism
Related to effective volume depletion
Glucocorticoid-remediable aldosteronism (GRA)
Apparent mineralocorticoid excess (AME)
Congenital adrenal hyperplasia
Tubulopathies
Bartter syndrome
Gitelman syndrome
Medications
Amphotericin B, cisplatin

potassium intake, transcellular redistribution of potassium, extrarenal potassium losses, and renal potassium losses (Table 14). Clinical history makes the etiology apparent and renders extensive diagnostic evaluation moot in many situations. Children with a history of recurrent hypokalemia, especially in the absence of accompanying acute illnesses, need to be carefully considered for underlying derangements in renal potassium handling.

Decreased Potassium Intake

By itself, decreased dietary intake of potassium is a rare cause of hypokalemia in children. Ongoing potassium restriction leads to activation of potassium conserving mechanisms, such as a reduction in the number of excretory potassium channels

(ROMK) within the renal tubule and resistance to the insulin-mediated intracellular flow of potassium [183]. Mild hypokalemia from simple decreased intake can, however, be exacerbated by diuretic use, diarrhea, or eating disorders such as anorexia or bulimia. States of chronic malnutrition are especially prone to severe hypokalemia if potassium loss is then superimposed. For instance, one report of malnourished children in Kenya demonstrated a baseline rate of hypokalemia of 10 % from decreased intake, but this increased more than threefold in the setting of concomitant diarrhea [184]. In hospitalized children, inadequate potassium intake may be a reflection of acute or chronic illness preventing sufficient provision of general nutrition, or there can be iatrogenic oversights such as the incorrect formulation of intravenous peripheral nutrition solutions. Keeping in mind concomitant clinical factors that may be influencing potassium balance should facilitate the provision of proper potassium supplementation.

Transcellular Redistribution of Potassium

Metabolic Alkalosis

Alkalosis promotes hypokalemia through two mechanisms. As systemic pH increases, hydrogen ions in the intracellular space move extracellularly to help blunt the alkalosis. To maintain electroneutrality, extracellular potassium then shifts intracellularly and this will be reflected by a fall in serum potassium levels.

With alkalosis, there is also increased potassium excretion in the urine. With the increase in serum bicarbonate, there is an increased load of bicarbonate filtered and eventually passed in the urine. Since a cation must accompany the filtered bicarbonate, this means that there are also increased urinary loads of potassium and sodium. Some of this potassium will get directly excreted along with the bicarbonate. Additionally, the increased concentration of sodium that is also presented to the distal nephron allows there to be more ready exchange of sodium for potassium in the distal nephron under the influence of aldosterone, with even further urinary potassium losses. This mechanism is most pronounced when there is

concomitant effective volume depletion from gastrointestinal losses or diuretic use or if hyperaldosteronism exists for other reasons.

Endocrine Effects

Transcellular redistribution of potassium can also arise from the effects of certain hormones. This is most commonly seen from the effects of insulin and from catecholamines with beta-adrenergic effects, both of which promote cell uptake of potassium. The ability of these substances to accomplish effective transcellular shift is underscored by the common use of both insulin and nebulized albuterol to treat hyperkalemia. Insulin-mediated hypokalemia can also be seen in children with refeeding syndrome or with eating disorders where insulin release may exacerbate a preexisting tendency towards hypokalemia from long-term poor nutritional intake. Children receiving intermittent nebulized albuterol are unlikely to present with significant alterations in serum potassium levels, but with continuous nebulization there can be a tendency for lower potassium levels to develop [185]. In critically ill children receiving intravenous catecholamines, either for bronchodilation or for hemodynamic reasons, there can be an augmented effect; up to 50 % of children with these treatments have been reported to develop hypokalemia [186].

In hyperthyroidism, hypokalemia can develop, mediated in part by increased expression and activity of the sodium–potassium ATPase [187]. Thyrotoxic periodic paralysis is a rare condition, almost always seen in adults, where patients with hyperthyrodism develop profound hypokalemia and ensuing muscle dysfunction.

This condition is in contradistinction to hypokalemic periodic paralysis caused by autosomal dominant mutations in voltage-gated calcium channels found in the skeletal muscle and in voltage-gated sodium channels at the neuromuscular junction. Affected individuals can present throughout childhood but especially in adolescence, have normal thyroid function, and often have their episodes of pronounced hypokalemia and paralysis instigated by an event causing insulin or adrenergic hormone release to initiate a fall in serum potassium levels that then gets exacerbated by their channelopathies.

Drugs

In addition to beta-adrenergic agents as discussed above, redistributive hypokalemia has also been described in chloroquine intoxication and also with the provision of risperidone and quetiapine [188, 189]. In children who have inadvertently ingested barium salts found in certain fireworks or rodent poisons, hypokalemia has also been described as a result of inhibition of normal potassium egress from cells [190, 191]. In these cases, the clinical history and consultation with local toxicology resources should help guide appropriate diagnosis and management.

Extrarenal Potassium Losses: Gastrointestinal Tract

Hypokalemia can evolve from upper or lower gastrointestinal tract losses, and gastrointestinal illness with unreplaced losses of potassium accounts for most cases of hypokalemia in otherwise healthy children. At up to 50 mEq/L, the potassium content of diarrhea is high compared to other body fluids, including vomit or gastric secretions [192]. Although both types of gastrointestinal loss can cause hypokalemia, the underlying pathophysiology differs.

With diarrheal illness, there are not only significant potassium losses from the stool, but with the evolution of concomitant volume depletion, an aldosterone-mediated kaliuresis can ensue. This can be exacerbated in the early phases of rehydration since, with improved effective circulating volume and augmented GFR, there will be increased delivery of filtered sodium to the distal nephron and more substrate for aldosterone-mediated potassium secretion.

In contrast, upper gastrointestinal losses from vomiting or nasogastic drainage may contain less than 10 mEq/L of potassium. The metabolic alkalosis that can develop from these losses will, however, lead to increased distal tubular delivery of sodium bicarbonate, and with the secondary upregulation of aldosterone from volume losses, the increased availability of sodium in distal tubular filtrate will allow for increased exchange for potassium and an effective kaliuresis.

Renal Potassium Losses

Increased Distal Sodium Delivery

Principal cells in the collecting duct contain apical epithelial cell sodium channels (ENaC) where sodium is reabsorbed under the influence of mineralocorticoid (primarily aldosterone) and exchanged electroneutrally for potassium via ROMK channels. For potassium excretion to occur effectively, sodium delivery to these nephron segments must be adequate and mineralocorticoid activity must be present. Increased delivery of sodium distally augments potassium excretion, especially in clinical situations where there are also effective circulating volume depletion and increased aldosterone activity. This physiology helps to account for the hypokalemia that can be seen with diuretic provision, with mannitol provision, with diabetic ketoacidosis, and, as explained above, with metabolic alkalosis from vomiting or nasogastric tube drainage.

Renal Tubular Acidosis

Both type 1 and type 2 RTA are associated with hypokalemia, although from varying physiologic mechanisms. With type 1 or distal RTA, the intrinsic inability of the distal nephron to acidify the urine by secreting hydrogen ions leads to potassium secretion to maintain electroneutrality. There may also be associated tubular cellular membrane permeability that allows for further potassium loss. With type 2 or proximal RTA, there is impaired proximal tubular reabsorption of filtered bicarbonate, leading to increased urinary losses of bicarbonate and associated cations. The increased distal tubular presentation of sodium facilitates potassium secretion, exacerbated by the aldosterone effect from any effective volume depletion caused by the augmented sodium and water losses.

Hyperaldosteronism

Normal physiologic stimuli for aldosterone secretion, most notably volume depletion, commonly play a contributing role to many of the causes of pediatric hypokalemia. In comparison, primary abnormalities in aldosterone secretion are rare in childhood, though certain inherited conditions can be seen, generally accompanied by hypertension. In autosomal dominant glucocorticoid-remediable aldosteronism, there is aldosterone synthase hyperactivity due to genetic mutations that allow aldosterone production to become regulated by ACTH. The provision of glucocorticoid suppresses the mineralocorticoid excess and ensuing high blood pressure and any associated hypokalemia [193]. In apparent mineralocorticoid excess (AME), cortisol degradation is impaired by genetic mutations that alter the efficacy of 11-beta-hydroxysteroid dehydrogenase, and cortisol can then bind to mineralocorticoid receptor and mediate signs and symptoms mimicking aldosterone excess. This same enzyme can be inhibited by glycyrrhizic acid that can be found in natural licorice and this explains why excess ingestion of natural licorice has been associated with hypokalemia as well. In forms of congenital adrenal hyperplasia such as 17-alpha-hydroxylase deficiency and 11-beta-hydroxylase deficiency, there can also be excess mineralocorticoid production and hypokalemia and hypertension.

Renal Tubulopathies

Certain genetic tubular disorders are characterized by impaired sodium reabsorption, increased distal tubular sodium delivery, and ensuing urinary potassium losses with the development of an associated alkalosis. In the various types of Bartter syndrome, abnormalities in the electrolyte transporters or channels in the thick ascending limb help mediate a kaliuresis and alkalosis as well as a tendency towards hypercalciuria. In Gitelman syndrome, the thiazide-sensitive sodium chloride symporter in the distal convoluted tubule is impaired, and there is often concomitant hypomagnesemia and normal or lower urinary calcium excretion. With both syndromes volume depletion and physiologic aldosterone stimulation will only serve to aggravate any underlying tendency to waste potassium in the urine, but provision of volume will not ameliorate baseline potassium wasting. In Liddle syndrome, gain-of-function mutations in ENaC result in dysregulated sodium reabsorption with ensuing hypertension, hypokalemia, and alkalosis as seen with more classic cases of mineralocorticoid excess.

Any Fanconi syndrome, whether idiopathic in etiology, related to drug exposure, or related to renal conditions such as cystinosis, can also result in hypokalemia as part of the diffuse proximal tubule solute losses that ensue. Children with hypokalemia from proximal tubular dysfunction will also lose large amounts of bicarbonate in their urine and will be prone to a metabolic acidosis, in distinction to the metabolic alkalosis that characterizes Bartter and Gitelman syndrome.

Drugs

Diuretics are by far and away the most commonly prescribed drug that can mediate hypokalemia through direct urinary potassium losses, by increasing distal sodium presentation, and by contributing to effective volume depletion and physiologic aldosterone activity. In addition, amphotericin and some chemotherapy drugs, most notably cisplatin, can also cause increased renal potassium wasting. With amphotericin, there is actual disruption of cellular membrane integrity and ensuing loss of potassium from the intracellular space. Some studies have suggested that up to half of the children receiving amphotericin will become hypokalemic, though the provision of liposomal amphotericin seems to substantially mitigate this problem [194]. With cisplatin, there can be direct tubular toxicity that interferes with the handling of potassium as well as wasting other electrolytes, with effects that can be quite long lived [195].

Diagnostic Evaluation

History and Physical Examination

The patient's history is important in guiding the diagnostic evaluation. An otherwise healthy child with hypokalemia accompanying an acute gastrointestinal illness requires less of an evaluation than a child with recurrent bouts of unexplained hypokalemia. Ascertaining any underlying predisposing medical conditions, medications, or dietary restrictions may help clarify the cause of the child's hypokalemia.

The physical examination should key on findings suggesting significant adverse effects from the low serum potassium such as cardiac arrhythmias or alterations in muscle tone or strength. There should also be some clinical assessment of effective circulating volume and respiratory effort, since severe abnormalities will influence immediate management decisions and may impact acid–base balance and, as a result, transcellular potassium distribution. Blood pressure should also be carefully measured since the presence or absence of hypertension helps distinguish certain of the renal tubulopathies.

Laboratory Testing

In the event that the cause of the hypokalemia is clear-cut – for instance vomiting with dehydration or diuretic therapy in the setting of poor potassium dietary intake – it is probable that follow-up assessment of serum potassium after proper therapy will show resolution of the problem and no reason to do further testing. On the other hand, in cases of less clear etiology, in cases of recurrent hypokalemia, or when hypokalemia recurs after initial supplementation is completed, there needs to be more specific assessment of renal handling of potassium to determine if there are inappropriate renal losses ongoing.

With profound hypokalemia (<2.5 mEq/L) and especially when there is evidence or suspicion of adverse cardiac effect, steps to ameliorate the hypokalemia should begin immediately and should not be delayed by further diagnostic evaluation. Fortunately, the blood and urine samples necessary to guide the evaluation can often be readily collected contemporaneously with initiation of therapy (Table 15).

Urine Potassium Quantification

A 24-h urine collection will give the most accurate assessment of the degree of urinary potassium losses since it can be directly compared to potassium intake to assess a net balance. Timed urine collections are difficult to perform in many children, so spot urine chemistries with concomitant serum chemistries are generally substituted and, in most cases, will provide enough information to allow for accurate assessment of renal response.

In the setting of a serum potassium level less than 3 mEq/L, random urinary potassium values

Table 15 Initial diagnostic studies to assess unexplained hypokalemia in children

Laboratory test	Key findings
Creatinine, electrolytes, phosphorus, magnesium	Derangement in addition to potassium
Venous pH	Systemic acidosis or alkalosis
Aldosterone and plasma renin activity	Variation from normal levels
Urinalysis	Appropriateness of pH and presence of glycosuria
Urine chemistries and urine creatinine (best done concomitantly with serum electrolytes and creatinine)	Urinary K excretion $\quad$ Random $U_K > 20$ mEq/L suggests renal loss $\quad$ $U_{K/Cr} > 15$ mEq/g suggests renal loss Hypercalciuria Urinary Cl excretion

Table 16 Hypokalemia and acid–base disorders

Hypokalemia and metabolic acidosis
$\quad$ Low urinary losses of potassium
$\qquad$ Diarrhea
$\quad$ High urinary losses of potassium
$\qquad$ Renal tubular acidosis
$\qquad$ Proximal tubulopathy (Fanconi or Fanconi like)
Hypokalemia and metabolic alkalosis
$\quad$ Low urinary losses of potassium
$\qquad$ Diuretics (chronically)
$\quad$ High urinary losses of potassium
$\qquad$ Hyperaldosteronism (often concomitant hypertension)
$\qquad$ Diuretics (acutely)
$\qquad$ Bartter syndrome (often concomitant hypercalciuria)
$\qquad$ Gitelman syndrome (often concomitant hypomagnesemia)

usually are less than 20 mEq/L and values significantly higher suggest renal wasting. Electrolyte concentration in a random urine void will be affected by water handling at that point in time, so spot samples in particularly dilute or concentrated samples may provide values that are lower or higher than if urine output were normal. Accordingly, urinary potassium-to-creatinine ratios can be done since urinary creatinine excretion is constant in children with normal renal function and this will correct for water excretion. In the setting of hypokalemia, a urine potassium-to-creatinine ratio <15 mEq/g creatinine (<1.5 mEq/mmol Cr) suggests the hypokalemia is not due to renal potassium wasting at that time and focus should shift to GI losses, poor intake, cellular shift, or prior diuretic use. Ratios >15 mEq/g creatinine suggest renal wasting.

Further Testing with Renal Potassium Wasting

In the setting of urinary potassium wasting, assessment of the child's blood pressure along with a few other specific urine and blood tests helps to clarify the reason for the kaliuresis. Specifically, a venous pH and serum electrolytes and serum magnesium level will allow the identification of an acid–base disorder, the presence of an anion gap, and the presence of hypomagnesemia.

Aldosterone and plasma renin activity will help determine if there is hyperaldosteronism. Urinary calcium excretion should also be measured to look for hypercalciuria. Urinary chloride levels will help in the differential diagnosis of hypokalemia with alkalosis (Table 16).

In the hypertensive child with urinary potassium wasting, both low blood aldosterone and renin levels should make apparent mineralocorticoid excess, Liddle syndrome, or a form of adrenal hyperplasia the most suspected pathologies. With high aldosterone but low renin levels, hyperaldosteronism should be suspected.

In the normotensive child with urinary potassium wasting, the presence of an acidosis suggests an RTA. With an alkalosis, urinary chloride levels less than 15 mEq/L speak to renal potassium wasting from volume depletion in the setting of a metabolic alkalosis as seen with emesis, nasogastric tube losses, or diuretics. With an alkalosis and higher urinary chloride levels, a renal tubulopathy such as Bartter or Gitelman syndrome is suspected. Hypercalciuria would point towards Bartter syndrome, and hypomagnesemia is more frequent with Gitelman, though genetic testing to clarify specific mutations and which channels or transporters are affected allows for there to be a better understanding if the potassium wasting arises from the thick ascending limb or the distal convoluted tubule.

Treatment of Hypokalemia in Children

Urgency of Potassium Supplementation

In patients with significant cardiovascular or respiratory compromise related to hypokalemia, management must proceed emergently and be focused on acutely increasing the serum potassium level by 0.3–0.5 mEq/L and then maintaining supplementation until a level of 3 mEq/L is reached. These interventions should proceed with ongoing cardiac monitoring to detect new or exacerbating arrhythmia.

Since intravenous potassium can be irritating to vessels, to prevent phlebitis or ongoing pain, concentrations exceeding 40 mEq/L are generally given centrally. When giving intravenous potassium, it is important for patient safety to limit the absolute amount of potassium available to be delivered in one single infusion in case the rate or volume of the infusion is inadvertently altered from what is intended. Hourly rates of infusion of 0.5–1 mEq/kg will generally result in serum potassium levels rising by nearly 0.5 mEq/L in the face of no new increased potassium losses.

Enteral Potassium Supplementation

In children with levels between 2.5 and 3 mEq/L and no clinical signs or symptoms of hypokalemia, potassium supplementation is warranted, although enteral supplementation is generally preferred to avoid the complications of intravenous provision. Although intravenous supplementation is commonly provided to critically ill children due to restrictions in enteral intake or other confounding factors, there is no evidence to suggest that enteral supplementation is inferior to its intravenous provision. In fact, a study of children in a pediatric cardiac intensive care unit showed that the provision of 1 mEq/kg of potassium either by intravenous or enteral routes resulted in no difference in efficacy or side effects, with both groups demonstrating an average improvement in serum potassium of 0.65 mEq/L [196].

Factors Influencing Efficacy of Supplementation

Concomitant administration of other medications that may alter renal potassium handling may affect individual response to potassium supplementation. For instance, the provision of amphotericin or furosemide to children receiving potassium supplementation results in more moderate increases in serum potassium because of urinary potassium losses. Conversely, children receiving ACE inhibitors often exhibit somewhat higher serum potassium levels after supplementation as a result of the effect of angiotensin blockade on GFR [197].

The type of potassium preparation given for supplementation can be tailored to the need for other specific electrolyte supplementation. Since many hypokalemic children have concomitant alkalosis with hypochloremia, potassium chloride is most frequently used for both enteral and intravenous supplementation. Potassium chloride supplements have also been shown to accomplish more efficient repletion than potassium phosphorus or potassium citrate or bicarbonate, although with concomitant acidosis or hypophosphatemia, their provision does make sense [198].

Any supplementation will be less effective if there are ongoing potassium losses that can continue to vary independently. In children with Bartter or Gitelman syndromes, use of potassium-sparing diuretics may help limit the extent of renal losses, and in those children with such tubulopathies and hypomagnesemia, magnesium provision can help blunt the attenuating effects of hypomagnesemia on potassium reabsorption [199].

Acid–Base Homeostasis

Acid–base homeostasis involves an intricate interplay between multiple regulatory mechanisms to maintain the extracellular arterial pH between 7.35 and 7.45. The typical diet for infants and children in much of the developed world is rich in animal proteins and cereal grain resulting in generation of net acid, as opposed to the generation of net base with vegetarian diets [200–202]. When adjusted for body weight, infants produce about 2–3 mEq/kg/day of nonvolatile acid, which is significantly higher than adults where the net nonvolatile acid production