Electrolyte Disorders: Derangements of Serum Sodium, Calcium, Magnesium, and Potassium

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Objectives:

- To review the basic physiology affecting sodium, water, calcium, magnesium, and potassium balance
- To recognize the common critical care syndromes and causes of deranged serum cations
- To become facile with the acute treatment of disordered cation balance

Key words: hypercalcemia; hyperkalemia; hypermagnesemia; hypernatremia; hyperosmolality; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypo-osmolality

Sodium

Water balance is measured by changes in osmolality. Osmolality is the number of osmotically active particles (osmoles) per liter of solution. (Osmolarity is expressed per kilogram). Hypo-osmolality indicates an excess of water relative to osmoles; hyperosmolality indicates water deficiency. The serum osmolality [in milliosmols per liter (mosm/L)] can be calculated by the following formula:

$$\text{Serum osmolality} = 2\,(Na^+ + K^+) + (\text{glucose}/18) + (\text{urea}/2.8)$$

where mosm is milliosmol, Na is sodium, and K is potassium; glucose and urea are given in mg/dL. The molecular weight of glucose is 180; urea, 28. Conversion from mg/dL to mosm/L yields 18 and 2.8.

One can see that serum osmolality is primarily due to the serum concentration of sodium and potassium (and their accompanying anions), glucose and urea. Of these, the serum sodium is most powerful, accounting for nearly 95% of serum osmolality. Therefore, *in most clinical circumstances, the serum sodium can be used as a surrogate for osmolality*. The serum sodium concentration has no direct relationship to the total body sodium, but rather, is an indicator of water balance relative to sodium.

Tonicity refers to the osmotic force (ability to move water across a semipermeable membrane) exerted by osmotically active particles. Hypotonic solutions will lose water to, and hypertonic solutions will gain water from an isotonic solution. Not all osmoles are equivalent in tonicity. Urea, for example, readily crosses cell membranes and exerts no tonic force. Glucose will induce water movement from most cells. The major extracellular osmole, sodium, is responsible for the variation in serum tonicity in most cases and, as such, is largely responsible for the volume of extracellular fluid (ECV). Therefore, *an excess of body sodium causes water movement into the extracellular space and obligates an increase in ECV, though not an increase in sodium concentration*.

Hyponatremia is not always equivalent to hypo-osmolality (Fig 1). By stimulating water movement into the ECV, hyperglycemia physiologically lowers serum sodium by 1.6 mEq/100 mg/dL glucose, causing hyponatremia with hyperosmolality. The same is true for hypertonic mannitol. Other molecules increasing serum osmolality, such as ethanol, isopropyl alcohol, ethylene glycol, and methanol, do not cause hyponatremia because of their small size and high membrane permeability (*ie*, they do not create an osmotic force or tonicity). They will, however, cause an osmolar gap defined as a > 20-mosm/L difference between the calculated and measured serum osmolality (Table 1). Hyperproteinemia (usually > 10 g/dL) and hyperlipidemia cause an increase in the solid phase of the blood volume, causing "hyponatremia" as the sodium

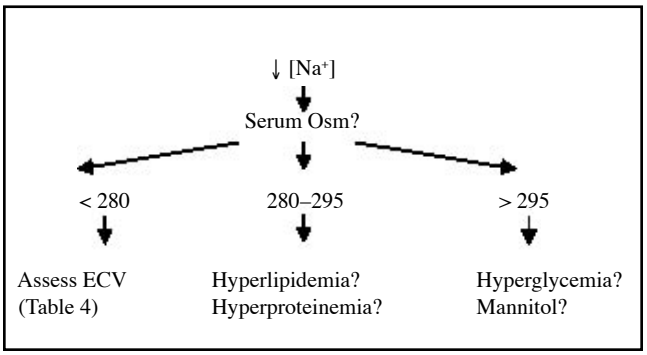

Figure 1. "Pseudohyponatremia" applies when hyponatremia does not reflect hypo-osmolality.

present is indexed to an artificially increased volume. The serum osmolality does not change. This pseudohyponatremia usually accounts for small changes in serum sodium (*eg*, 1 mEq sodium/460 mg/dL lipid).

In most clinical situations (pseudohyponatremia excepted), the serum sodium is directly related to the serum osmolality such that hyponatremia indicates an excess and hypernatremia a deficiency of water relative to total body sodium. The characteristics of body sodium and water balance are outlined in Table 2.

Regulation of Sodium Balance

As the major extracellular cation and osmole, sodim largely determines ECV. Changes in total body sodium are reflected as changes in the ECV and are best assessed clinically by physical findings. Therefore, rales, jugular venous distention, edema, and an S3 gallop indicate excess ECV and body sodium. Tachycardia, hypotension, flat neck veins in the supine position, dry mucous membranes, and skin tenting indicate ECV and body sodium depletion. In neither case will the serum sodium concentration necessarily change. Thus, *neither the total body sodium nor ECV is directly related to the serum sodium concentration.*

Table 1. *Differential Diagnosis of an Elevated Osmolar Gap**

With Anion-Gap Acidosis	Without Acidosis
Ethylene glycol	Isopropyl alcohol
Methanol	Diethyl ether
Formaldehyde	Mannitol
GFR < 10 mL/min	Severe hyperproteinemia
Paraldehyde	Severe hyperlipidemia

*The osmolar gap = measured – calculated osmolality. Calculated serum osmolality = $2(Na^+ + K^+)$ + glucose(mg/dL)/18 + BUN(mg/dL)/2.8.

Table 2. Characteristics of Sodium and Water Balance*

	Sodium	Water
Distribution	Extracellular volume	Total body water
Assessment	Physical examination	Serum osmolality
	Urinary Na, FENa	Serum sodium
		UOsm , COsm
Regulation	GFR	Thirst
	Aldosterone	ADH
	"Third factors"	Renal handling of water

*UOsm, urinary osmolality. COsm, osmolar clearance.

Ordinarily, renal sodium loss balances dietary sodium intake. The renal excretion of sodium is dependent on the glomerular filtration rate (GFR), aldosterone, and a variety of "third factors" that affect renal tubular reabsorption of filtered sodium. These include natriuretic peptides (atrial natriuretic peptide, brain natriuretic peptide), the renin angiotensin system, norepinephrine, prostaglandins, and intraglomerular and peritubular Starling forces. The GFR in turn is dependent on renal blood flow, the transglomerular capillary hydrostatic and oncotic pressures and the permeability of the glomerular capillary wall. The afferent and efferent glomerular arteriolar sphincters largely determine intraglomerular Starling forces (transglomerular capillary hydrostatic pressure and transglomerular capillary oncotic pressure). Aldosterone enhances distal tubular sodium reabsorption coupled to hydrogen ion (H^+) and potassium secretion. Normally, approximately 99% of filtered sodium is reabsorbed. The 1% excreted sodium is best measured by the fractional excretion of sodium (FENa).

Regulation of Water Balance

Thirst, antidiuretic hormone (ADH), and the kidneys control water balance. Hypothalamic receptors for hyperosmolality and hypovolemia stimulate thirst and ADH secretion. While hyperosmolality is the more common stimulus, hypovolemia is more potent. For example, a hypovolemic patient will

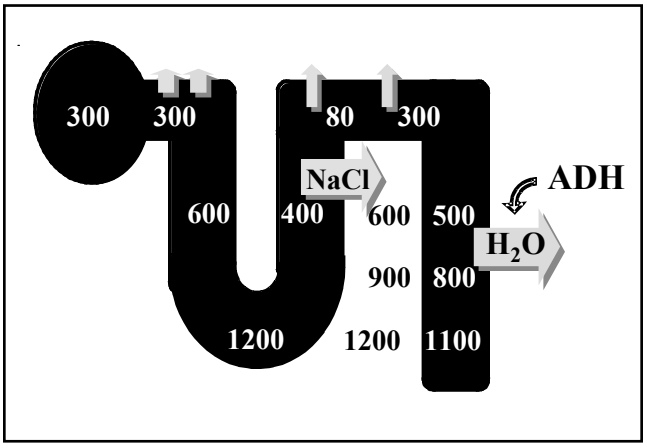

Figure 2. The renal handling of water. Water reabsorption (urinary concentration) requires the presence of ADH and a concentrated medullary interstitium provided by active Na^+ and Cl^- reabsorption in the ascending limb of Henle. Water excretion (urinary dilution) occurs in the absence of ADH. GFR and proximal tubular reabsorption affect urinary concentration and dilution by controlling the delivery of glomerular filtrate to the loop and distal nephron. (Numbers reflect osmolality.)

continue to secrete ADH despite hypo-osmolality and hyponatremia. ADH exerts its primary effect by enhancing renal water reabsorption across the collecting tubule, thus concentrating the urine (Fig 2). This passive reabsorption of water is dependent on the presence of a more highly concentrated renal medullary interstitium caused by active sodium and chloride reabsorption from the ascending limb of Henle. Sodium (but not water) reabsorption from the late ascending limb and early distal tubule dilutes the filtrate and generates free water. Free water excretion occurs in the absence of ADH. Both the GFR and proximal tubular reabsorption rate affect free water excretion (urine dilution) and reabsorption (urine concentration) as these factors control the quantity of glomerular filtrate delivered to the downstream nephron segments.

Clinical Disorders of Sodium Balance (Disorders of the ECV)

ECV Depletion: Hemorrhage, GI sodium loss, or renal sodium loss can deplete the ECV. Usually the sodium loss is isotonic. For example, the sodium concentration in diarrhea is approximately 120 mEq/L. In emesis, depending on the pH, it varies from 60 to 120 mEq/L. Coupled with insensible losses, therefore, the serum sodium changes little in most cases where GI sodium loss depletes the ECV. In fact, the predominant electrolyte disturbance is hypokalemia, which is associated with metabolic acidosis in cases of diarrhea, metabolic alkalosis with vomiting, or a balanced acid-base status where diarrhea and vomiting coexist.

Diuretics are the most common cause of renal salt wasting. Again, these are isosmotic losses, usually not associated with changes in the serum sodium concentration. Certainly, severe hyponatremias are reported with diuretics, but these are idiosyncratic (in the case of thiazide diuretics) or associated with an underlying disorder of sodium retention such as heart failure. Hypoaldosteronism will cause renal sodium loss and isotonic ECV depletion. If coupled to glucocorticoid deficiency, mild hyponatremia can occur. Various renal tubular defects can also cause "salt-losing" nephropathy. This is not uncommon, but it is usually relatively mild with several types of chronic interstitial nephritis. Very rare causes of renal sodium loss include Bartter's syndrome and renal tubular acidosis (RTA). Again, the volume lost in these cases is approximately isosmolar so that serum sodium concentration is either unchanged or mildly decreased. The major clinical feature is ECV depletion, determined by physical examination.

Basic fluid therapy for ECV depletion is isotonic crystalloid. When blood and/or colloid are needed, they are converted to "crystalloid equivalents" at a ratio of 3:1. The volume of replacement can be estimated by a percentage of total body water. (The effect of sodium is on total body water [TBW], although its distribution is extracellular.) Mild, moderate, or severe volume losses approximate 5, 10 or 15% of TBW depending on the rapidity with which they occurred. (See Table 3). The rate of replacement depends on the degree of hemodynamic instability.

ECV Expansion: The classic causes of ECV excess are the "edematous disorders": congestive heart failure (CHF), cirrhosis (with ascites), and nephrosis (nephrotic syndrome). Renal failure (decreased GFR) and hyperaldosteronism are other causes of sodium retention. Physical findings of ECV excess such as rales, jugular venous distension, ascites, and edema are usually present. When mild, the serum sodium is usually normal in these syndromes. When hyponatremia does occur, it is a marker of disease severity.

Several mechanisms are responsible for the renal sodium retention seen in these edematous disorders. The GFR is often low as a result of poor cardiac output or decreased oncotic pressure. Aldosterone excess and its effect to increase distal tubular sodium reabsorption is a secondary result. Increased levels of circulating or regionally generated angiotensin II cause preferential constriction of the efferent glomerular sphincter, lowering the hydrostatic pressure while raising the oncotic pressure in the peritubular capillary, thus enhancing proximal renal tubular sodium retention. These factors override

Table 3. *Signs and Symptoms of ECV Depletion Roughly Correlate to a Percentage of TBW**

ECV Depletion	Mild	Moderate	Severe
TBW depletion	5%	10%	15%
Symptoms	"Dry"	Lethargy	Stupor
Heart rate	80	100	120
BP	Normal	Orthostatic	Shock
Jugular vein	Normal	< 5 cm H_2O	Flat
Skin	Normal		Tenting

*The severity of symptoms and the urgency of replacement are affected by the acuity of the underlying disease.

the increased production and effects of natriuretic peptides such that the urinary sodium and FENa are extremely and inappropriately low.

The basic fluid therapy for patients with ECV excess is salt and water restriction.

Clinical Disorders of Water Balance

Hyponatremia: As a surrogate for serum osmolality, the serum sodium reflects changes in water balance relative to total body sodium. Therefore, after excluding pseudohyponatremia (see above), one can best approach hyponatremia based on the patient's ECV (Table 4).

Hyponatremia occurs with ECV depletion whenever free water intake accompanies GI or renal sodium loss. The most common example is a GI illness with continued oral or IV water (without salt) replacement. Another example is diuretic-associated hyponatremia. Although it is usually mild, severe hyponatremia can occur, particularly with thiazide-type diuretics. Thiazides limit free water excretion by inhibiting distal tubular sodium reabsorption. ECV depletion appropriately stimulates ADH secretion and water reabsorption, contributing to the hyponatremia. Loop diuretics, on the other hand, gradually diminish medullary interstitial solute and osmolarity, thereby limiting the osmolar gradient for water reabsorption so that hyponatremia is less commonly a side effect of these agents. Elderly women and patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) are particularly prone to thiazide-induced hyponatremia. Polydipsia and hypokalemia contribute to the pathogenesis. Treatment is to discontinue thiazides, restrict water, and replace potassium.

Isotonic saline solution is indicated for those patients with moderate to severe volume depletion. Care must be taken to avoid too rapid a correction of hyponatremia. Because ADH secretion is abrogated as saline solution is replaced, a physiologic water diuresis will correct the hyponatremia promptly. Hypertonic saline solution is rarely necessary.

Hyponatremia with a normal ECV occurs whenever the addition of free water to the ECV exceeds the renal capacity to excrete water. In normal patients, 10 to 15 L of water intake is required to cause significant hyponatremia. Extreme polydipsia (psychogenic polydipsia) is rare, but hyponatremia can occur with significantly less water intake if ADH secretion is stimulated or its renal tubular effect is enhanced by certain drugs (Table 5). Chronic malnutrition or "low osmolar syndrome" is a much less dramatic cause of hyponatremia. These disorders will have appropriately dilute urine (specific gravity, < 1.010; urinary osmolality, < 200).

The syndrome of inappropriate antidiuretic hormone (SIADH) also causes hyponatremia in euvolemic patients. In fact, edema is an exclusion criterion for SIADH, as are hypothyroidism and cortisol deficiency. Features include hypo-osmolality with relatively high urinary osmolality (less than maximally dilute urine or > 100 mosm/L) and hyponatremia with relatively high urinary sodium (> 30 mEq/L). Excluding the edematous disorders (heart, liver, and kidney disease) is also a prerequisite for the diagnosis of SIADH.

Table 4. *Differential Diagnosis of Hyponatremia and Hypo-osmolality**

	Hypovolemia (↓ ECV)		Euvolemia (Normal ECV)		Hypervolemia (↑ ECV)
Diagnosis	Vomiting, diarrhea, fistula	Diuretics, hypo-aldosteronism, RTA,	Polydipsia, malnutrition	SIADH, hypothyroid, hypocortisol	CHF, cirrhosis/ascites, nephrotic syndrome, renal failure
UOsm, mosm/L	> 300	300	< 100	>100	>300†
UNa, mEq/L	< 20	> 20	> 30	> 30	<10†
Other findings	Hypokalemia: vomiting, diarrhea, diuretics, RTAsteronism Hyperkalemia: hypoaldosteronism Metabolic alkalosis: Vomiting, diuretics Metabolic acidosis: diarrhea, hypoaldosteronism		Hypokalemia: SIADH, polydipsia Hyperkalemia: hypocortisol Hypouricemia		
Fluid Therapy	Isotonic saline solution		Restrict H_2O		Restrict H_2O and saline solution

*UOsm = urine osmolality; UNa = urine sodium.
† Excludes renal failure.

The basic fluid therapy for polydipsia or SIADH is sodium and water restriction. Drugs that inhibit ADH effect are useful therapeutic adjuncts. These include demeclocycline, phenytoin, lithium, and loop diuretics (by limiting medullary interstitial osmoles).

Table 5. Differential Diagnosis of SIADH

Drugs
Amitriptyline
Bromocriptine
Carbamazepine
Chlorpropamide
Cisplatin
Cyclophosphamide
Haloperidol
MAO inhibitors
Methylenedioxymethamphetamine
NSAIDs
Serotonin reuptake inhibitors (fluoxetine, etc.)
Thioridazine
Thiothixene
Vincristine/vinblastine
Malignancy
Small cell lung
Other lung
Pancreas
Several others
CNS Diseases
Cerebrovascular accident
Infection
Trauma
Pulmonary
Pneumonia
Atelectasis
Asthma
Pneumothorax
Major Surgery
Transphenoidal

Hyponatremia marks the severity of the edematous disorders, particularly CHF. The decrease in "effective" intravascular volume stimulates thirst, increases ADH secretion, limits GFR, and enhances proximal renal tubular reabsorption of sodium and water, thus limiting delivery of glomerular filtrate to the diluting ascending limb. The result is increased intake and limited excretion of free water. Hyponatremia is also commonly seen in patients with cirrhosis (particularly those with ascites) and nephrotic syndrome. The urinary sodium is low (< 20 mEq/L) and the urinary osmolarity is high (> 300 mosm/L), mimicking ECV depletion, although with very different physical findings. Basic fluid therapy for these disorders is salt and water restriction with diuretics.

Hypernatremia: Because thirst provides excellent protection against hyperosmolality, hypernatremia is unusual unless access to water is impaired. Therefore, hypernatremic patients are usually elderly, have a decreased mental status, or are in some way incapacitated. The fact that hypernatremia mandates hypertonicity ensures cellular dehydration, particularly of the brain. Therefore, hypernatremic patients are usually quite ill. Because hypernatremia is synonymous with hyperosmolality, a water deficit relative to sodium is always present. Therefore, an approach to the hypernatremic patient based on his or her salt balance (ECV) is appropriate (Table 6, Fig 3).

Hypernatremia in patients with decreased ECV occurs with osmotic cathartics and diuretics. The osmotic effect ensures that water will be lost

Table 6. *Differential Diagnosis of Hypernatremia**

Hypovolemia (↓ ECV)		Euvolemia (Normal ECV)	Hypervolemia (↑ ECV)		
Diagnosis	GI loss: vomiting, diarrhea, fistula	Renal loss: hyperglycemia, mannitol, high-protein feedings, postobstructive diuresis	Sweating, hypodipsia	Central DI, nephrogenic DI	Hypertonic $NaHCO_3$, hypertonic saline solution, sea water ingestion
UOsm, mosm/L	> 800	300–800	> 800	< 300†	> 800
UNa, mEq/L	< 20	> 30	< 20	< 20	>30
Other Findings	Hypokalemia: vomiting, diarrhea, diuresis Metabolic alkalosis: vomiting			UOsm after AVP: central DI, 400–800†, nephrogenic DI, no change	
Fluid Therapy	Combined water and saline solution		Water	Water	

*UOsm = urine osmolality; UNa = urine sodium; AVP = aqueous vasopressin, 5 U subcutaneously.
†Urine osmolality varies with partial vs complete DI.

in excess of sodium and potassium (because of the presence of another osmole). This occurs with lactulose or sorbitol in the intestinal tract or in the urine with hyperglycemia, mannitol, low-molecular-weight proteins (from hyperalimentation), and urea (postobstructive diuresis). The osmotic effect also causes variable salt depletion. Fluid therapy for these patients, therefore, requires water (to correct the free water deficit) and isotonic saline solution (to correct the decreased ECV).

Euvolemia with hypernatremia indicates isolated loss of free water. This can occur with massive insensible losses such as severe sweating or hyperventilation or, rarely, with primary hypodipsia. The most common cause of euvolemic hypernatremia, however, is diabetes insipidus (DI). These patients have an inappropriately low ADH level (central DI) or a blunted ADH effect (nephrogenic DI). The urinary osmolality is inappropriately low (<300 mosm/L), despite hypernatremia. Patients with central DI will respond to parenteral administration of ADH by increasing urinary osmolality and decreasing urinary volume. Both central and nephrogenic DI can occur in either partial or complete forms and, therefore, a broad range of urinary osmolalities can be seen following water deprivation or ADH. The differential diagnosis of both central and nephrogenic DI is listed in Table 7.

The rarest clinical salt and water problem is hypernatremia with increased ECV. This occurs with massive administration of hypertonic bicarbonate or hypertonic saline solution, or rarely in those with salt-water ingestion. The urinary osmolality is high and the patients are appropriately excreting increased urinary sodium. Treatment is obviously to restrict the salt and administer free water and diuretics as needed.

Figure 3 plots the common derangement of body salt (disorders of the ECV) and water (disorders of serum osmolality). Most of the clinical syndromes seen in critically ill patients are actually combinations of separate salt (ECV) and water problems. When this occurs, it is helpful to approach each patient as if he has two separate problems. First, define the nature and treatment of the ECV problem. Next, identify the water (osmolality) problem and its treatment. Finally, sum and administer the therapies. This approach will simplify even the most severe derangement of fluid and electrolytes.

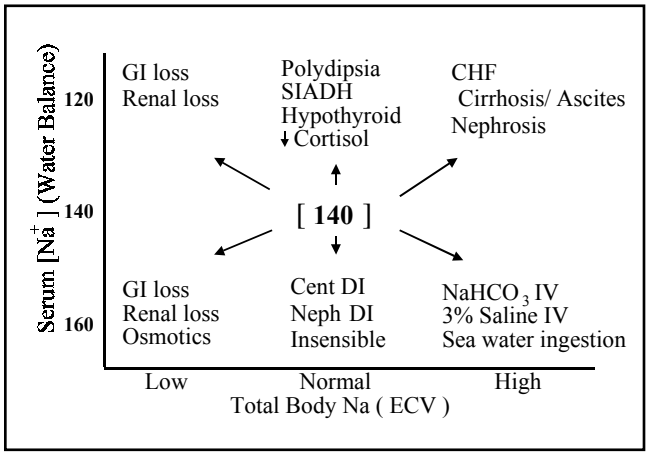

Figure 3. Differential diagnosis of hypo- and hypernatremia based on water balance relative to total body sodium (ECV). Cent = central; Neph = nephrogenic.

Treatment Issues

The serum osmolality is the major determinant of brain water and therefore brain volume (Fig 4). Abrupt hypo-osmolality causes brain edema; abrupt hyperosmolality causes brain shrinkage. The more rapidly this occurs, the more likely symptoms will occur and the more urgent is the need for therapy. Over time, adaptation to changes in osmolality occurs. With chronic hypo-osmolality, the brain loses electrolytes (osmolytes), thus lowering intracellular osmolality to that of plasma. With hyperosmolality, the brain will generate osmoles (idiogenic osmoles), thus raising intracerebral osmolality. Both adaptations tend to return brain osmolality toward plasma osmolality and brain volume towards normal as a new steady state is reached. Any subsequent change in plasma osmolality (*ie*, those induced by therapy)

Table 7. *Differential Diagnosis of Central and Nephrogenic DI*

Central DI	Nephrogenic DI
Trauma	Drugs
Neurosurgery	Lithium
Transphenoidal	Demeclocycline
Pituitary infarction	Amphotericin
Sheehan's	Cisplatin
Cerebrovascular accident	Glyburide
Shock	Hypercalcemia
Neoplasm	Hypokalemia
Meningitis/encephalitis	Tubulointerstitial nephritis
Drugs	Obstructive uropathy
Phenytoin	Diuretic-phase acute tubular necrosis
Ethanol	
Familial	

will cause brain swelling or shrinkage once again. Potential complications of this include altered mental status, seizures, coma, or the most serious complication, central pontine myelinolysis. Therefore, slow correction is the rule for severe degrees of either hypo- or hypernatremia.

For asymptomatic patients with hyponatremia, simple water restriction and observation are adequate. If the patient is hyponatremic and ECV depleted, isotonic saline solution can be given. Again, because ADH secretion is volume sensitive, too-rapid correction can occur as saline solution is administered; thus, frequent monitoring of the serum Na is required.

For patients who are severely symptomatic with hyponatremia, hypertonic (3%) saline solution is indicated to increase the serum Na by not more than 0.5 to 1 mEq/L/h and not more than 12 mEq/L in a 24-h period. One can calculate the sodium deficit in these patients as follows:

Na deficit = (desired Na – current Na) × TBW

TBW is approximately 60% of body weight in men and 50% of body weight in women and in the elderly. Using this formula, a 70-kg man with a serum Na of 103 mEq/L would need 504 mEq of Na to raise his serum Na to 115 mEq/L (12 mEq/L × 42 L). This is approximately 3.3 L of isotonic saline solution (154 mEq/L) or approximately 1 L of 3% saline solution (513 mEq/L). Again, close observation for too-rapid correction or signs of fluid overload is mandatory in these patients.

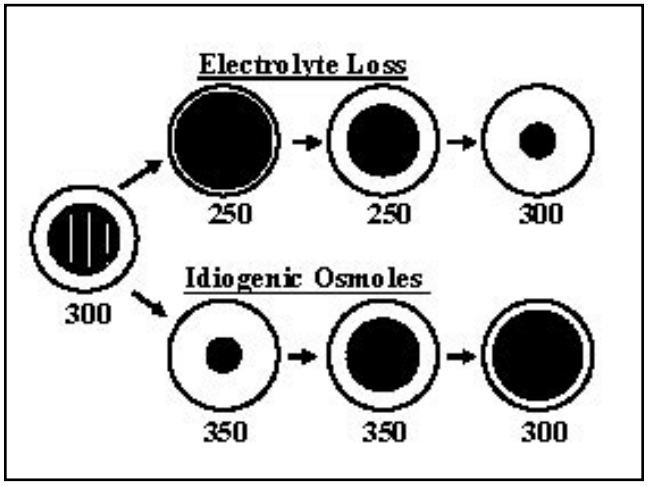

Figure 4. Acute change in serum osmolality effects intracerebral swelling or shrinkage. Within days, a new steady state is reached by brain electrolyte loss (in response to hypo-osmolality) or the generation of osmoles (in response to hyperosmolality). Too-rapid correction of serum osmolality will similarly effect a change in cerebral volume.

For hypernatremia, the water deficit can be calculated as follows:

Water deficit = [(current Na ÷ target Na) – 1] × (0.6 × body weight in kg)

For example, a 60-kg man with a serum Na of 175 mEq/L needs 9 L of free water to correct his serum Na to 140 mEq/L [(175 ÷ 140) – 1 × 36 L = 9L]. As with hyponatremia, correction should not exceed 0.5 to 1 mEq/L/h and not more than 12 mEq/L in a 24-h period in severely hypernatremic patients.

An excellent approach to fluid therapy for either hypo- or hypernatremia is to determine the effect of 1 L of a given fluid on serum [Na^+] as outlined by the following formula:

Change [Na^+] = {(infusate $Na^+ + K^+$) – serum [Na^+]} / (TBW + 1)

In our above example, 1 L of dextrose 5% in water would decrease the patient's serum [Na^+] by 4.7 mEq/L [(0 – 175) ÷ 37 = 4.7]. By this formula, it would require 7.5 L to decrease his serum Na^+ from 175 mEq/L to 140 mEq/L. This formula easily adjusts for any potassium administered. Use of this formula requires knowledge of the Na^+ content of commonly prescribed IV fluids. These are outlined in Table 8, along with their percent distribution into the ECV.

Calcium

Calcium balance is depicted in Figure 5. Approximately 400 mg (30 to 35% of an average daily intake of 1,200 mg) is absorbed from the intestinal tract. Daily excretion of this amount occurs in the urine and stool (150 to 200 mg/d in each). Vitamin D is the major factor controlling absorption. The fat-soluble vitamin D_3 is absorbed from the diet, 25-hydroxylated in the liver (to calcefediol), and 1-hydroxylated by the kidney to 1,25 dihydroxy vitamin D (calcitriol), the active form of the vitamin. Parathyroid hormone (PTH) and hypophosphatemia primarily stimulate the formation of calcitriol.

Table 8. *Sodium Content and Percent Distribution Into the ECV of 1 L of Crystalloid Solutions*

Infusate	Na^+ (mEq)	% in ECV
Dextrose 5% in water	0	40
0.2% normal saline solution	34	55
0.45% normal saline solution	77	73
Lactated Ringer's solution	130	97
0.9% normal saline solution	154	100

Malabsorption, liver disease, and renal disease may cause vitamin D deficiency.

PTH preserves serum calcium by stimulating osteoclast resorption of bone, increasing renal tubular reabsorption of filtered calcium, and stimulating the production of calcitriol, which enhances intestinal absorption of calcium. PTH secretion is stimulated by ionized hypocalcemia and suppressed by hypercalcemia and hypomagnesemia. It is primarily the combined action of PTH and vitamin D on bone that controls serum calcium.

In the blood, approximately 40 to 50% of calcium is in the ionized or physiologically active form. In critically ill patients, total serum calcium is a poor predictor of ionized calcium. Albumin binding, alkalosis, and the presence of chelators such as citrate, phosphate, or lactate can significantly influence the ionized fraction with relatively little alteration of total calcium (Table 9). In fact, *pseudohypercalcemia* refers to the elevation of serum total calcium due to hyperalbuminemia. Similarly, low levels of serum albumin will lower serum total calcium. In neither case will the active or ionized calcium change. This direct relationship of total calcium to albumin can be quantitated: Δ albumin 1 g/dL =Δ total calcium 0.8 g/dL. Direct measurement of ionized calcium by ion-specific electrodes may be necessary in certain cases.

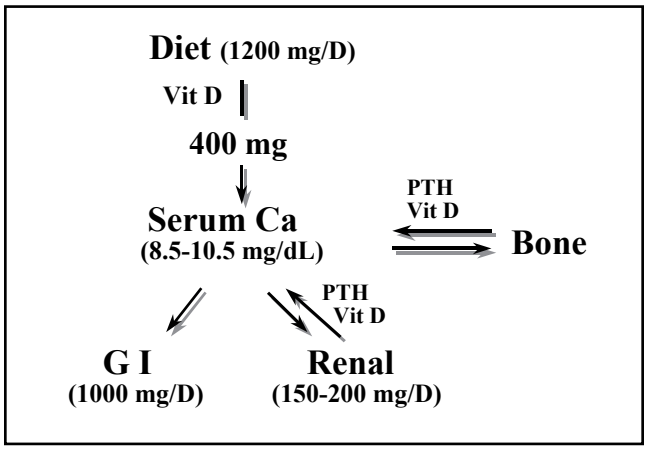

Figure 5. Calcium balance.

Hypercalcemia

Hypercalcemia (Table 10) can occur with excessive GI absorption (milk alkali syndrome, excess vitamin D) or with increased renal reabsorption of filtered calcium (hyperparathyroidism, thiazides). However, clinically significant hypercalcemia most often occurs with accelerated bone resorption. In hyperparathyroidism, direct osteoclast activation by PTH causes hypercalcemia. PTH or PTH-related peptides (PTHrP) can also be produced by several malignancies (lung, ovary, kidney, bladder). Osteoclast-activating factor, produced by myeloma cells, also causes hypercalcemia. Hypercalcemia caused by direct lytic involvement of bone is seen with several cancers (breast, prostate). Immobilization can cause hypercalcemia by increasing bone resorption, particularly in young patients or those with Paget's disease. Hypercalcemia is common in the recovery phase of rhabdomyolysis-induced acute renal failure. Severe hypercalcemia [> 14 mg/dL (3.5 mmol/L)] usually requires a combination of factors, including excessive osteoclast-stimulated bone resorption, increased renal tubular calcium reabsorption (due to PTH, PTHrP, or volume depletion), and immobilization. This combination is most often seen in patients with malignancy in the ICU setting.

The clinical manifestations of hypercalcemia include anorexia, constipation, and abdominal pain progressing to weakness, lethargy, obtundation, and

Table 9. *Common Clinical Conditions That Dissociate Total (TCa) and Ionized (ICa) Calcium**

Condition	TCa	ICa	Explanation	Degree
Hypoalbuminemia	↓	N	Decreased protein binding	Δ Alb 1.0 mg/dL = Δ TCa 0.8 mg/dL
Hyperalbuminemia	↑	N	Increased protein binding	Δ Alb 1.0 mg/dL = Δ TCa 0.8 mg/dL
Multiple myeloma	↑	N	Ca binding to globulin	
Respiratory alkalosis	N	↓	Increased albumin binding	Δ pH 0.1 = Δ ICa 0.16 mg/dL
Hyperparathyroidism	N	↑	Decreased albumin binding	
Hyperphosphatemia	N	↓	Chelation	
Hypercitratemia	N	↓	Chelation	

*N = normal; Alb = albumin.

even coma as the serum calcium increases to 16 mg/dL. Polyuria due to nephrogenic DI may produce volume depletion, which in turn stimulates renal tubular calcium reabsorption and aggravates hypercalcemia. Renal insufficiency is common with acute and/or severe hypercalcemia. A shortened QT interval, bradycardia, and heart block may occur, particularly in patients taking digitalis.

Treatment of mild hypercalcemia (<12 mg/dL) may require only simple hydration, restriction of dietary calcium, and treatment of the underlying disease. As serum calcium increases above 12 mg/dL or the patient becomes symptomatic, specific anticalcemic therapy may be required (Table 11). IV saline solution (3 to 4 L/d) and furosemide (80 to 160 mg/d) can produce a modest decrement in serum calcium by enhancing renal calcium excretion. When using saline solution and furosemide, one should achieve a minimum urinary output of 100 mL/h. Corticosteroids (hydrocortisone 200 to 300 mg/d IV or prednisone 40 to 80 mg/d, po) are effective when hypercalcemia is caused by excess vitamin D (vitamin D intoxication, sarcoidosis, lymphoma) or multiple myeloma.

More aggressive treatment is required for serum calcium >14 mg/dL. Although relatively weak, calcitonin (4 to 8 U/kg q6-12h) can work within hours to lower serum calcium. Calcitonin is also a potent analgesic and therefore particularly suited for patients with bone pain. Usually, treatment with mithramycin (25 μg/kg IV) or the bisphosphonates (etidronate, 7.5 mg/kg IV; pamidronate, 30 to 90 mg IV; zolendronic acid, 4 to 8 mg IV) will also be necessary. Mithramycin will begin to lower serum calcium within hours, with its nadir effect at 48 to 72 h. The effect typically persists for several days, but repeat dosing is often necessary. The effect of bisphosphonate therapy is usually slower but more prolonged, with a nadir in serum calcium at 7 days and a duration of several weeks. Zolendronic acid (4 to 8 mg IV) is likely superior to pamidronate. A constant infusion of gallium nitrate (200 mg/m^2/d for 5 days) will normalize serum calcium in 70 to 80% of hypercalcemic patients. The onset, however, is relatively slow and the nadir is usually at 8 to 10 days. Use of gallium is limited by its nephrotoxicity. The use of oral (too weak) and IV (too dangerous) phosphate is no longer recommended for treatment of hypercalcemia. Hemodialysis or peritoneal dialysis with a zero-calcium dialysate is rarely necessary but can be used to treat severe hypercalcemia.

Table 10. *Common Causes of Hypercalcemia*

Increased GI absorption
Vitamin D intoxication
Ectopic vitamin D
Lymphoma
Sarcoidosis
Histoplasmosis
Tuberculosis
Increased bone resorption
Primary hyperparathyroidism
Ectopic PTH, PTHrP
Osteolytic metastases
Multiple myeloma (osteoclast-activating factor)
Immobilization
Posthypocalcemic (*eg*, rhabdomyolysis)
Increased renal reabsorption
Hyperparathyroidism
Thiazide diuretics

Table 11. *Treatment of Hypercalcemia**

Therapy	Dose	Onset	Duration	Efficacy	Toxicity
NS	3–6 L/D	Hours	Hours	1–2 mg/dL	Excess ECV
Furosemide	80–160 mg/d	Hours	Hours	1–2 mg/dL	ECV depletion
Hydrocortisone	200 mg/d	Hours	Days	Mild‡	↑BP, ↓K, ↑glucose
Calcitonin	4–8 U/kg	Hours	Hours	1–2 mg/dL	Nausea, thrombopenia
Mithramycin	25 μg/kg	12 h	Days	1–5 mg/dL	Marrow, liver, kidney
Pamidronate	30–90 mg/wk	Days	1–4 wk	1–5 mg/dL	Fever
Zolendrate§	4–8 mg	Days	Weeks	1–5 mg/dL	
Gallium	200 mg/m^2	Days	Days to weeks	1–5 mg/dL	Fever

* NS = normal saline solution; K, potassium.
† Expected decrease in serum calcium.
‡ Effective for hypercalcemia of vitamin D excess or ectopic vitamin D syndromes.
§ Preferred bisphosphonate.

Hypocalcemia

Hypocalcemia (Table 12) can be seen with vitamin D deficiency, PTH deficiency or resistance, or binding by various intravascular or tissue chelators. Malabsorption of calcium and vitamin D is most commonly from small-bowel resection or inflammation (*eg*, Crohn's disease). Liver disease (decreased synthesis of calcefediol) or renal disease (decreased synthesis of calcitriol) may also cause vitamin D deficiency. Hypoparathyroidism most often occurs postthyroidectomy, but rarely is due to a familial multiglandular condition. Suppression of PTH release is usually due to hypomagnesemia (see below) but may accompany severe hypermagnesmia, sepsis, burns, pancreatitis, or rhabdomyolysis. Hypomagnesemia also causes PTH resistance. Rapid or massive blood or plasma transfusion may cause calcium chelation by citrate, an effect also seen when citrate is used as an alternative anticoagulant for hemodialysis. The most common calcium chelator, however is phosphorus, and this hypocalcemic syndrome may occur in patients with major tissue damage (burns, rhabdomyolysis), tumor lysis syndrome, or acute and chronic renal failure.

Table 12. *Common Causes of Hypocalcemia*

- Decreased GI absorption
  - Vitamin D deficiency
    - Malabsorption
    - Hepatic failure
    - Renal failure
  - Malabsorption syndromes
- Decreased bone resorption
  - Hypoparathyroidism
    - Postthyroidectomy
    - Familial
    - Hypomagnesemia
    - Sepsis
    - Burns
    - Pancreatitis
    - Rhabdomyolysis
  - PTH resistance
    - Hypomagnesemia
    - Pseudohypoparathyroidism
  - Osteoblastic metastases
- Intravascular or tissue chelation
  - Citrate
    - Transfusion
    - Anticoagulation
  - Albumin
  - Fat embolus
  - Hyperphosphatemia
    - Burns
    - Rhabdomyolysis
    - Tumor lysis
    - Renal failure

The clinical signs of hypocalcemia include perioral paresthesia, muscular spasms, tetany, and even seizures. Chvostek's and Trousseau's signs do not usually develop unless the serum calcium falls below 6 mg/dL. Several studies suggest that ionized hypocalcemia and elevated PTH are associated with an increased mortality. Prolongation of the QT interval is common. Bradycardia and hypotension are indications for emergent therapy.

Because treatment of hypocalcemia with calcium alone is only transiently effective, one must identify and correct the underlying cause. Mild or asymptomatic hypocalcemia requires only an increase in dietary calcium. IV calcium (100 to 200 mg IV over 10 min followed by 100 mg/h constant infusion) should be reserved for symptomatic patients or those with serum calcium < 6 mg/dL. Calcium gluconate (90 mg elemental calcium per 10 mL ampule) is preferred to limit vein irritation and extravasation. Calcium infusion should be avoided in patients with severe hyperphosphatemia. Serum calcium should initially be monitored every 4 h. Once the serum calcium is > 7 mg/dL, it usually can be maintained with oral calcium supplements (0.5 to 1.0 g tid). The addition of vitamin D3 (25,000 to 50,000 units three times weekly), calcefediol (25-[OH]D3) (50 to 300 μg/d) or calcitriol (1,25 (OH)2 D3) (0.25 to 1 μg/d) will be necessary in those patients with vitamin D deficiency. Thiazide diuretics, by inducing intravascular volume contraction, increase proximal tubular calcium reabsorption and can serve as a therapeutic adjunct. Finally, the hypocalcemia of magnesium depletion cannot be corrected until magnesium losses are replaced.

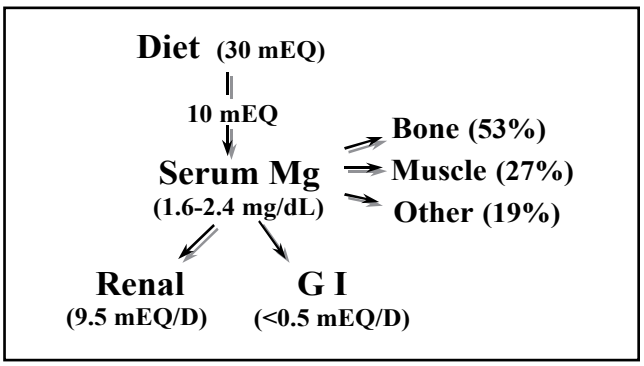

Figure 6. Magnesium balance.

Magnesium

One third of the approximately 360 mg (30 mEq) daily dietary magnesium is absorbed (Fig 6). Renal excretion accounts for most of the daily magnesium loss, but some GI secretion occurs as well. Like calcium, magnesium is primarily an intracellular cation stored in bone (55%) and skeletal muscle (30%). Less than 1% of total body magnesium is in the extracellular fluid (ECF). Unlike calcium, however, no hormones control magnesium balance, and the serum magnesium is not readily exchangeable with tissue stores. Therefore, loss of magnesium can lead rather quickly to hypomagnesemia, and there is little protection against hypermagnesemia when renal excretion is impaired.

Hypermagnesemia

Hypermagnesemia occurs primarily in patients with renal insufficiency or in those receiving excess magnesium by IV (treatment of pre-eclampsia), rectal (magnesium-containing enemas), or oral (antacids, laxatives) routes. The latter occurs more commonly when absorption is enhanced by GI inflammation (ulcer, gastritis, colitis). Excess dietary magnesium will not cause hypermagnesemia unless renal function is impaired.

The signs and symptoms of hypermagnesemia are related to the plasma level (Table 13). Lethargy and hyporeflexia can occur at levels > 4 mg / dL. Respiratory depression, bradycardia, and hypotension are usually seen at > 7 mg / dL. A serum magnesium > 12 mg / dL can cause muscle paralysis, complete heart block, and cardiac arrest. In these cases, IV calcium (100 to 200 mg of elemental calcium over 5 to 10 min) can be life-saving. Dialysis can also be used when renal function is impaired. Milder symptoms and magnesium levels < 8 mg / dL require only volume expansion and discontinuing exogenous magnesium.

Table 13. *Clinical Manifestations of Hypo/hypermagnesemia Related to the Serum Level*

Serum Level (mg / dL)	Manifestations
> 12	Muscle paralysis, complete heart block, cardiac arrest
> 7	Somnolence, respiratory depression, hypocalcemia, bradycardia, hypotension
> 4	Lethargy, hyporeflexia
1.6–4	Usually asymptomatic
< 2	"Normomagnesemic magnesium depletion"
< 1.6	Weakness, anorexia, hypokalemia, hypocalcemia
< 1.2	Tetany, positive Chvostek's and Trousseau's signs, wide QRS, peaked T
< 0.8	Convulsions, prolonged PR, ventricular arrhythmia

Hypomagnesemia

Hypomagnesemia occurs in 12% of hospitalized patients but in 40 to 60% of ICU patients. It predicts excess mortality in acutely ill and postoperative adult patients and in neonates with ventilatory failure. Treatment of hypomagnesemia improves survival in some studies of endotoxic shock (rats), patients with acute myocardial infarction (MI), and postoperative patients with left ventricular dysfunction.

GI and renal losses account for most cases of magnesium depletion (Table 14). Extreme diarrhea or malabsorption can readily deplete serum magnesium; prolonged vomiting or gastric secretion induces hypomagnesemia more gradually. Because of obligate daily losses of magnesium in the stool

Table 14. *Common Causes of Hypomagnesemia*

- GI losses
  - Malabsorption
  - Diarrhea
  - Gastric suction
  - Prolonged dietary restriction
- Renal losses
  - Excessive IV fluids
  - Postobstructive diuresis
  - Recovery-phase acute tubular necrosis
  - Drugs
    - Diuretics
    - Aminoglycosides
    - Alcohol
    - Amphotericin
    - Cyclosporine
    - Platinum
  - Ketoacidosis
  - Bartter's syndrome
  - Renal tubular acidosis
- Increased cellular uptake
  - Refeeding
  - Recovery from hypothermia
  - Insulin
  - Rapid tumor growth
  - Rhabdomyolysis
  - Pancreatitis

and urine, a 1- to 2-week period of not eating or not receiving magnesium in IV fluids will cause hypomagnesemia in most patients.

Renal magnesium wasting occurs with excessive diuresis (IV fluids, postobstructive, diuretic phase of acute renal failure), diuretic drugs (loop and thiazide diuretics) and with several drugs (Table 14). Renal magnesium loss can easily be distinguished from GI losses by demonstrating an elevated fractional excretion of magnesium (FEMg >1.5%) in a hypomagnesemic patient. The calculation must account for the plasma (P) protein binding of magnesium as follows:

$$FEMg = (UMg \times PCr \times 100)/[(0.7 \times PMg) \times UCr]$$

where UMg is urinary magnesium, PCr is plasma creatinine, PMg is plasma magnesium, and UCr is urinary creatinine.

Hypomagnesemia can result with increased cellular uptake from several causes, including refeeding, insulin therapy, or tissue injury (rhabdomyolysis). Acute pancreatitis can cause hypomagnesemia by saponification.

The clinical manifestations of magnesium depletion are roughly correlated with the plasma level (Table 13). Weakness, anorexia, and neuromuscular irritability can progress to respiratory depression and convulsions in severe cases. The cardiac toxicity is highly dependent on concurrent myocardial perfusion such that severe arrhythmias may occur with seemingly mild hypomagnesemia in the setting of acute MI. Hypokalemia (due to renal potassium wasting) and hypocalcemia (due to altered PTH resistance and release) occurs in as many as 40% of magnesium-deficient patients (trication deficiency). Neither the hypokalemia nor hypocalcemia of magnesium deficiency can be corrected without magnesium repletion. In fact, hypokalemia and hypocalcemia in the ICU patient often corrects with magnesium administration, even in normomagnesemic patients (normomagnesemic magnesium depletion).

Treatment of hypomagnesemia includes correcting the underlying GI or renal cause. Serious complications such as ventricular ectopy, hypokalemia, or hypocalcemic tetany require IV magnesium sulfate (1 g [8 mEq] IV stat followed by 6 g over 24 h). Because serum levels normalize before tissue stores are repleted, renal losses of magnesium usually continue, necessitating daily magnesium replacement (6 to 8 g magnesium sulfate) for 3 to 5 days. Milder cases of hypomagnesemia can be treated by slow-release tablets (Table 15). Amiloride will increase magnesium absorption in the cortical collecting tubule and is an excellent adjunct to magnesium therapy.

The use of magnesium to prevent arrhythmias and improve survival in patients with acute MI remains controversial and is not routinely recommended. However, in high-risk patients, 16 mEq (8 mmol/L, 192 mg) of magnesium IV over 5 to 15 min prior to reperfusion (thrombolysis or angioplasty) with 128 mEq (64 mM, 1,536 mg) over the ensuing 24 h appears to decrease the incidence of arrhythmia and left ventricular dysfunction and improve mortality. It is contraindicated in patients with a greater than first-degree heart block or bradycardia, as magnesium can delay atrioventricular conduction.

Potassium

Although 2% of total body potassium is in the ECF, serum potassium is in dynamic equilibrium with intracellular stores. Movement into and out of cells is controlled by the adrenergic nervous system, insulin, and alterations in pH. Daily dietary intake (100 mEq) is matched by daily renal (90 mEq) and GI (10 mEq) excretion. Like calcium and magnesium, alterations in serum potassium are best explained by changes in intake, cellular shift, and renal excretion (Fig 7).

Table 15. *Treatment of Hypomagnesemia*

Serum Mg (mg/dL)	Clinical Situation	Treatment	Elemental Mg mg	mM	mEq
≥ 1.6	Chronic depletion	Magnesium oxide 400 mg bid	241	10	20
≥ 1.6	Prolonged IV fluids	$MgSO_4$ 4 g/d IV	400	16	32
1.2–1.6	Minimal signs/symptoms	$MgSO_4$ 8 g/d IV	800	32	64
< 1.2	Hyperreflexia, myoclonus	$MgSO_4$ 6 g IV q6-8h	600	25	50
< 1.2	Ventricular arrhythmias	$MgSO_4$ 2 g IV over 15 min	200	8	16

Hyperkalemia

The causes of hyperkalemia are outlined in Table 16. Because the kidney is able to substantially increase potassium excretion (up to 300 mEq daily), excess dietary potassium rarely causes hyperkalemia. However, in patients with even mild renal impairment, excessive potassium intake may be an important cause of hyperkalemia. Besides oral potassium supplements, occult sources of potassium include potassium penicillin, salt substitutes, stored blood, and oral (chewed) tobacco products.

Hyperkalemia is often due to release of cellular potassium. Nonselective β-blockers (*eg*, propranolol) may elevate serum potassium by this mechanism. Aldosterone deficiency increases serum potassium by causing an intra- to extracelluar potassium shift and by decreasing renal excretion. Insulin deficiency and hypertonicity (*eg*, hyperglycemia) independently cause cellular-to-serum shift of potassium, which explains the hyperkalemia (and the prompt resolution with therapy) so often seen in diabetic ketoacidosis. Hyperchloremic acidosis (but not organic acidoses—*eg*, ketoacidosis, lactic acidosis) is also associated with hyperkalemia due to cellular shifts. In these cases, the serum potassium increases by an average of 0.5 mEq/L for each 0.1 decrement in pH. Finally, cell lysis can present a potentially huge potassium burden to the ECF. Thus, life-threatening hyperkalemia can be seen with rhabdomyolysis, tumor lysis syndrome, massive hemolysis, and occasionally with succinylcholine, particularly with simultaneous renal insufficiency.

The most common causes of hyperkalemia are related to decreased renal excretion. Because the renal tubules not only reabsorb nearly all potassium filtered at the glomerulus, but also secrete most of the 90 mEq of potassium excreted daily, hyperkalemia rarely develops from renal failure (low GFR) *per se*. Rather, "renal" hyperkalemia is usually due to some defect in tubular potassium secretion. Tubular secretion of potassium requires aldosterone, good-functioning distal and collecting tubular cells, and an adequate delivery of filtered sodium and water to these nephron segments. Thus, any cause of hypoaldosteronism (hyporeninemia, isolated aldosterone deficiency, angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin-receptor blockers, heparin) predisposes to hyperkalemia. Hyperkalemia frequently accompanies tubulointerstitial renal diseases (particularly chronic pyelonephritis, an-

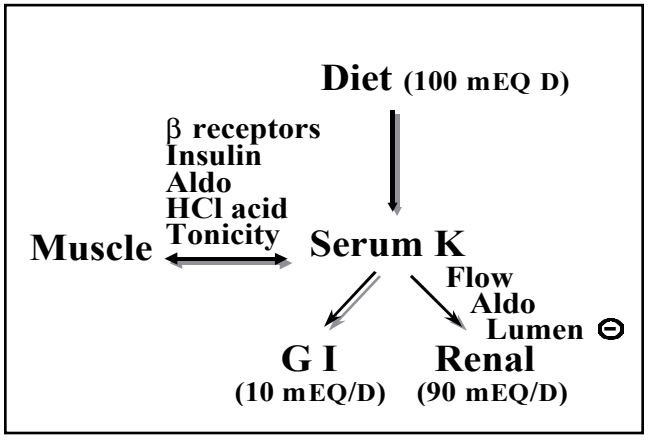

Figure 7. Potassium balance. Aldo = aldosterone.

Table 16. *Common Causes of Hyperkalemia*

Excess intake (usually only with renal insufficiency)
Potassium supplements
Salt substitutes
Potassium penicillin
Stored blood
Oral tobacco products
Intra- to extracellular shift
β_2-blockers
Aldosterone deficiency
Insulin deficiency
Hypertonicity
Succinylcholine
Hyperchloremic acidosis
Cell lysis
Tumor lysis syndrome
Hemolysis
Rhabdomyolysis
Decreased renal excretion
Decreased GFR (< 5 mL/min)
Decreased tubular secretion
Hypoaldosteronism
Primary
Hyporeninemic
Heparin
ACEIs/angiotensin-receptor blockers
Tubulo-interstitial nephritis
Analgesic nephropathy
Pyelonephritis
Sickle-cell nephropathy
Renal transplant nephropathy
Obstructive nephropathy
Drugs
Amiloride
Spironolactone
Triamterene
Cyclosporine
Tacrolimus
Trimethoprim
Pentamidine
NSAIDs

algesic nephropathy, sickle-cell disease, transplant rejection, and obstructive uropathy) despite relative preservation of renal function (GFR > 20 mL/min). The failure to simultaneously secrete hydrogen ion allows hyperchloremic (nonanion-gap) acidosis frequently to accompany hyperkalemia (type IV RTA). Finally, several drugs cause hyperkalemia by inhibiting tubular potassium secretion. In addition to potassium-sparing diuretics (spironolactone, triamterene, and amiloride), cyclosporine, tacrolimus, high-dose trimethoprim, pentamidine, NSAIDs, and ACEIs all share this potential complication.

Pseudohyperkalemia is the release of potassium when blood clots in a test tube. Patients with severe leukocytosis (>100,000) or thrombocytosis (> 400,000) are particularly prone to this phenomenon. This diagnosis is confirmed by a simultaneously drawn serum (red-top) and plasma (green-top) potassium level.

The toxicity of hyperkalemia is neuromuscular and cardiac. Paresthesias and weakness may progress to flaccid paralysis. ECG changes include peaked T waves in the precordial leads followed by decreased R-wave amplitude, widened PR interval, widened QRS complex, and finally loss of the P wave and the development of the sine wave. Heart block or ventricular standstill may occur at any point. The correlation between the serum potassium and the ECG is quite variable.

The treatment of hyperkalemia is outlined in Table 17. When the serum potassium is < 6 mEq/L, little therapy is required other than discontinuing the occult sources of dietary potassium listed in Table 16. As the potassium rises to > 6 mEq/L and/or peaked T waves appear, volume expansion (as tolerated), loop diuretics, and oral sodium polystyrene sulfonate powder (Kayexalate; Sanofi Winthrop Pharmaceuticals; New York, NY) are appropriate. (Kayexalate via rectum is reported to cause colonic necrosis.) Although somewhat slow to act, these treatments actually increase potassium excretion. When more urgent therapy is needed for hyperkalemia (> 7 mEq/L), driving potassium intracellularly with glucose and insulin (25 to 50 g dextrose with 10 to 20 U of regular insulin) or the β-agonist albuterol (5 to 20 mg [1.0 to 4.0 mL] inhaled) is indicated. Albuterol usually works within 30 min, will lower the serum potassium by 0.6 to 1.0 mEq/L, and lasts for 2 h or more. Calcium therapy (10 mEq IV over 5 min) is reserved for hyperkalemia-induced heart block, the sine wave, or of course ventricular arrest. Its effect is immediate but short-lived (< 60 min). Other maneuvers to remove potassium from the body (such as diuretics or Kayexalate) must be promptly initiated as well. Dialysis (usually hemodialysis) can also be employed to remove potassium.

Hypokalemia

The causes of hypokalemia are listed in Table 18. Significant GI loss of potassium is usually colonic (diarrhea, cathartic abuse) and accompanied by a hyperchloremic acidosis. Although gastric juice contains very little potassium (10 mEq/L), vomiting or gastric suction often causes hypokalemia due to concurrent volume contraction, secondary hyperaldosteronism, and renal potassium wasting. This also explains the renal hydrogen ion secretion and the seemingly "paradoxic aciduria" of contraction alkalosis. Renal artery stenosis (secondary hyperaldosteronism) causes hypokalemia due to urinary potassium loss. Renal wastage is also seen when nonreabsorbable anions (*eg*, carbenicillin) are

Table 17. *Treatment of Hyperkalemia*

Serum K (mEq/L)	ECG Δ	Treatment	Onset	Duration	Mechanism
< 6	None	Avoid NSAIDs Restrict dietary K			
> 6	Peaked T	ECV expansion	Hours		
	Prolonged PR	Loop diuretic IV	1–2 h	Hours	Renal excretion
		Kayexalate po	2–4 h	Hours	GI excretion
> 7	Widened QRS	Glucose/insulin IV	Minutes	Hours	Redistribution
		Albuterol (inhaled)	Minutes	Hours	Redistribution
		$NaHCO_3$ IV*	Minutes	Hours	Redistribution
> 8	Sine wave	Calcium	1–3 min	< 1 h	Cardiac

*Most useful with simultaneous hyperchloremic acidosis.

filtered into the urine, increasing distal potassium secretion. Any process increasing tubular flow (diuretics, diuretic phase of acute renal failure, postobstructive diuresis) will enhance tubular potassium secretion. Renal tubular acidosis (type I and II) and Bartter's syndrome are rare causes of renal hypokalemia. Hypomagnesemia is a more common cause of hypokalemia due to renal potassium loss.

Hypokalemia caused by extra- to intracellular shift usually accompanies refeeding or treatment of hyperglycemia with insulin. Hypokalemia may cause a wide range of clinical manifestations. Muscle weakness (including respiratory muscles), myalgias, cramps, and even rhabdomyolysis can occur. Gastroparesis, ileus, and constipation are common features. Hypokalemia may also cause nephrogenic DI, renal phosphate wasting, and acidification defects due to decreased ammonia production. The most serious hypokalemia toxicity, however, is cardiac. Isolated premature ventricular contractions, ventricular tachycardia, delayed conduction, enhancement of digitalis toxicity, and various ECG changes (U waves, flat T waves, ST-segment depression, and atrioventricular block) may all occur.

Potassium replacement can be done via the enteral or IV route. Potassium with chloride or other anions (citrate, bicarbonate, phosphate) is effective orally or via a gastric tube and can be given with impunity as long as renal function is normal. With more severe degrees of hypokalemia or in patients symptomatic from hypokalemia, rapid correction may be accomplished intravenously. When potassium is > 2 mEq/L and there are no ECG changes, 10 mEq/h is sufficient; 40 mEq/h can be given with cardiac monitoring if the serum potassium is < 2 mEq/L. Peripheral infusions should be concentrated to ≤ 60 mEq/L and administered through as large a vein as possible. Central infusions are best administered into the superior vena cava.

One must remember the necessity of treating coexistent magnesium depletion in hypokalemic patients.

Table 18. *Common Causes of Hypokalemia*

GI losses
Diarrhea
Cathartics
Enteric fistula
Villous adenoma
Extra- to intracellular shift
Insulin therapy
Refeeding
β-Agonists
Periodic paralysis
Renal losses
Hyperaldosteronism
Adrenal adenoma
Cushing's syndrome
Vomiting/gastric suction
Renal artery stenosis
Exogenous steroids
Licorice
Nonabsorbable anions
Carbenicillin
Ticarcillin
Piperacillin
Ketones
Increased urine flow
Diuretics
Renal tubular acidosis
Bartter's syndrome
Magnesium depletion

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Notes

Notes