Hypernatremia represents a deficit of water in relation to the body’s sodium stores, which can result from a net water loss or a hypertonic sodium gain (Table 1). Net water loss accounts for the majority of cases of hypernatremia.\(^\text{9-11}\) It can occur in the absence of a sodium deficit (pure water loss) (Fig. 1B) or in its presence (hypotonic fluid loss) (Fig. IC and 1D). Hypertonic sodium gain usually results from clinical interventions or accidental sodium loading (Table 1 and Fig. 1E).

Because sustained hypernatremia can occur only when thirst or access to water is impaired, the groups at highest risk are patients with altered mental status, intubated patients, infants, and elderly persons.\(^\text{1,6}\) Hypernatremia in infants usually results from diarrhea, whereas in elderly persons it is usually associated with infirmity or febrile illness.\(^\text{6,13,14}\) Thirst impairment also occurs in elderly patients.\(^\text{15,16}\) Frail nursing home residents and hospitalized patients are prone to hypernatremia because they depend on others for their water requirements.\(^\text{7}\)

**CLINICAL MANIFESTATIONS**

Signs and symptoms of hypernatremia largely reflect central nervous system dysfunction and are prominent when the increase in the serum sodium concentration is large or occurs rapidly (i.e., over a period of hours).\(^\text{1,6}\) Most outpatients with hypernatremia are either very young or very old.\(^\text{17}\) Common symptoms in infants include hyperpnea, muscle weakness, restlessness, a characteristic high-pitched cry, insomnia, lethargy, and even coma.\(^\text{5,13}\) Convulsions are typically absent except in cases of inadvertent sodium loading or aggressive rehydration.\(^\text{14,18,19}\) Unlike infants, elderly patients generally have few symptoms until the serum sodium concentration exceeds 160 mmol per liter.\(^\text{15,20}\) Intense thirst may be present initially, but it dissipates as the disorder progresses and is absent in patients with hypodipsia.\(^\text{5}\) The level of consciousness is correlated with the severity of the hypernatremia.\(^\text{9}\) Muscle weakness, confusion, and coma are sometimes manifestations of coexisting disorders rather than of the hypernatremia itself.

Unlike hypernatremia in outpatients, hospital-acquired hypernatremia affects patients of all ages.\(^\text{7}\) The clinical manifestations are even more elusive in hospitalized patients because they often have preexisting neurologic dysfunction. As in children, rapid sodium loading in adults can cause convulsions and coma.\(^\text{5,21}\) In patients of all ages, orthostatic hypotension and tachycardia reflect marked hypovolemia.

Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death. Brain shrinkage is countered by an adaptive response that is initiated promptly and consists of solute gain by the brain that tends to restore lost water. This response leads to the normalization of brain volume and accounts for the milder symptoms of hypernatremia that develops slowly (Fig. 2).\(^\text{22-24}\) However, the normalization of brain volume does not occur.
The mortality rate associated with hypernatremia varies widely according to the severity of the condition and the rapidity of its onset. It is difficult, however, to separate the contribution of hypernatremia to mortality from the contribution of underlying illnesses.11,23

MANAGEMENT

Proper treatment of hypernatremia requires a two-pronged approach: addressing the underlying cause and correcting the prevailing hypertonicity.3,11 Managing the underlying cause may mean stopping gastrointestinal fluid losses; controlling pyrexia, hyperglycemia, and glucosuria; withholding lactulose and diuretics; treating hypercalcemia and hypokalemia; moderating lithium-induced polyuria; or correcting the feeding preparation. In patients with hypernatremia that has developed over a period of hours (e.g., those with accidental sodium loading) rapid correction improves the prognosis without increasing the risk of cerebral edema, because accumulated electrolytes are rapidly extruded from brain cells.11,22 In such patients, reducing the serum sodium concentration by 1 mmol per liter per hour is appropriate.11 A slow-

![Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hypernatremia.](image-url)
allowance for these losses must also be made. In ad-
tory or incidental, will aggravate the hypernatremia,
ongoing losses of hypotonic fluids, whether obliga-
which we recommend a targeted fall in the serum
creas by 4.8 mmol per liter. The goal of treatment
retention of 1 liter of dextrose will reduce
planned. The estimated volume of total body water
body weight is 68 kg. Hypernatremia caused by pure
sodium concentration is 168 mmol per liter, and the
sodium concentration is 10 mmol per liter over a period of
proximately 10 mmol per liter over a period of
hours. Therefore, 2.1 liters of the solution (10 ÷ 4.8)
is required. With 1.5 liters added to compensate for
average obligatory water losses over the 24-hour pe-
rone of 1 liter of any infusate.
Because the risk of cerebral edema increases with the
infusate, the lower the infusion rate required.
chloride (one-half isotonic saline). The more hypoton-
sodium chloride (isotonic saline) is unsuit-
ids should be given intravenously. Only hypotonic
oral route or a feeding tube; if neither is feasible, flu-
convulsant therapy and adequate ventilation.

The preferred route for administering fluids is the
oral route or a feeding tube; if neither is feasible, flu-
ids should be given intravenously. Only hypotonic
fluids are appropriate, including pure water, 5 percent
dextrose, 0.2 percent sodium chloride (referred to as
one-quarter isotonic saline), and 0.45 percent sodium
chloride (one-half isotonic saline). The more hypoton-
ic the infusate, the lower the infusion rate required.
Because the risk of cerebral edema increases with the
volume of the infusate, the volume should be re-
stricted to that required to correct hypertonicity. Except
in cases of frank circulatory compromise, 0.9 percent
sodium chloride (isotonic saline) is unsuitable
for managing hypernatremia.

After selecting the appropriate infusate, the physi-
cian must determine the rate of infusion. This can
be easily calculated with the use of a formula (formu-
la 1 in Table 2) that estimates the change in the se-
rum sodium concentration caused by the retention
of 1 liter of any infusate. The required volume of in-
fusate, and hence the infusion rate, is determined by
dividing the change in the serum sodium concentra-
tion targeted for a given treatment period by the val-
ue obtained from formula 1. Table 2 also shows the
sodium concentrations of commonly used infusates,
their fractional distribution in the extracellular fluid,
and clinical estimates of total body water. The cases
described below illustrate the various forms of hy-
pernatremia and their management.

Pure Water Loss

A 76-year-old man presents with a severe obtun-
dation, dry mucous membranes, decreased skin tur-
gor, fever, tachypnea, and a blood pressure of 142/82
mm Hg without orthostatic changes. The serum so-
dium concentration is 168 mmol per liter, and the
body weight is 68 kg. Hypernatremia caused by pure
water depletion due to insensible losses is diagnosed
(Fig. 1B), and an infusion of 5 percent dextrose is
planned. The estimated volume of total body water
is 34 liters (0.5 × 68). According to formula 1, the
retention of 1 liter of 5 percent dextrose will reduce
the serum sodium concentration by 4.8 mmol per liter
(\(10 - 168\) ÷ (34 + 1) = -4.8). The goal of treatment
is to reduce the serum sodium concentration by ap-
proximately 10 mmol per liter over a period of 24
hours. Therefore, 2.1 liters of the solution (10 ÷ 4.8)
is required. With 1.5 liters added to compensate for
average obligatory water losses over the 24-hour pe-
rone of 3.6 liters will be administered for the
next 24 hours, or 150 ml per hour. The serum glu-
cose concentration will be monitored, with insulin
therapy started at the first indication of hyperglyce-
mia, a complication that would aggravate the hyper-
tonicity. Close monitoring of the patient’s clinical
status and laboratory values, initially at intervals of

<table>
<thead>
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<td><strong>Net water loss</strong></td>
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<td>Pure water</td>
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<td>Unreplaced insensible losses (dermal and respiratory)</td>
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<td>Hypodipsia</td>
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<td>Neurogenic diabetes insipidus</td>
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<tr>
<td>Post-traumatic</td>
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<td>Caused by tumors, cysts, histiocytosis, tuberculosis, sarcoidosis</td>
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<td>Idiopathic</td>
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<tr>
<td>Caused by aneurysms, meningitis, encephalitis, Guillain–Barre’s syndrome</td>
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<td>Caused by ethanol ingestion (transient)</td>
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<td>Congenital nephrogenic diabetes insipidus</td>
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<td>Acquired nephrogenic diabetes insipidus</td>
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<td>Caused by renal disease (e.g., medullary cystic disease)</td>
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<td>Caused by hypercalcemia or hypokalemia</td>
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<td>Caused by drugs (lithium, demeclocycline, fosarnet, methoxyltrane, amphotericin B, vasopressin V₂ receptor antagonists)</td>
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<tr>
<td>Hypotonic fluid</td>
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<td>Renal causes</td>
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<td>Burns</td>
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<td>Ingestion of sodium chloride</td>
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<td>Ingestion of sea water</td>
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<td>Sodium chloride–rich emetics</td>
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<td>Hypertonic saline enemas</td>
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<td>Intravenous injection of hypertonic saline</td>
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<td>Hypertonic sodium chloride infusion</td>
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<td>Hypertonic dialysis</td>
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<tr>
<td>Primary hyperaldosteronism</td>
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<tr>
<td>Cushing’s syndrome</td>
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er pace of correction is prudent in patients with hy-
pernatremia of longer or unknown duration, because
the full dissipation of accumulated brain solutes oc-
curs over a period of several days (Fig. 2). In such
patients, reducing the serum sodium concentration
at a maximal rate of 0.5 mmol per liter per hour
prevents cerebral edema and convulsions. Consequently, we recommend a targeted fall in the serum
sodium concentration of 10 mmol per liter per day
for all patients with hypernatremia except those in
whom the disorder has developed over a period of
hours. The goal of treatment is to reduce the serum
sodium concentration to 145 mmol per liter. Since
ongoing losses of hypotonic fluids, whether obliga-
tory or incidental, will aggravate the hypernatremia,
allowance for these losses must also be made. In ad-
dition, patients with seizures require prompt anti-
convulsant therapy and adequate ventilation.

The preferred route for administering fluids is the
oral route or a feeding tube; if neither is feasible, flu-
ids should be given intravenously. Only hypotonic
fluids are appropriate, including pure water, 5 percent
dextrose, 0.2 percent sodium chloride (referred to as
one-quarter isotonic saline), and 0.45 percent sodium
chloride (one-half isotonic saline). The more hypoton-
ic the infusate, the lower the infusion rate required.
Because the risk of cerebral edema increases with the
volume of the infusate, the volume should be re-
stricted to that required to correct hypertonicity. Except
in cases of frank circulatory compromise, 0.9 percent
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ue obtained from formula 1. Table 2 also shows the
sodium concentrations of commonly used infusates,
their fractional distribution in the extracellular fluid,
and clinical estimates of total body water. The cases
described below illustrate the various forms of hy-
pernatremia and their management.
six to eight hours, will guide adjustments in the administration of fluids.

**Hypotonic Sodium Loss**

A 58-year-old woman with postoperative ileus is undergoing nasogastric suction. She is obtunded and has diminished skin turgor and mild orthostatic hypotension. The serum sodium concentration is 158 mmol per liter, the potassium concentration is 4.0 mmol per liter, and the body weight is 63 kg. Hypernatremia caused by hypotonic fluid loss is diagnosed (Fig. 1C), and an infusion of 0.45 percent sodium chloride is planned, with the goal of decreasing the serum sodium concentration by 5 mmol per liter over the next 12 hours. Although there is evidence of a depletion in the volume of extracellular fluid, the patient’s hemodynamic status is not sufficiently compromised to warrant the initial use of 0.9 percent sodium chloride. The estimated volume of total body water is 31.5 liters (0.5 × 63). It is estimated that the retention of 1 liter of 0.45 percent sodium chloride will reduce the serum sodium concentration

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**Figure 2. Effects of Hypernatremia on the Brain and Adaptive Responses.**

Within minutes after the development of hypertonicity, loss of water from brain cells causes shrinkage of the brain and an increase in osmolality. Partial restitution of brain volume occurs within a few hours as electrolytes enter the brain cells (rapid adaptation). The normalization of brain volume is completed within several days as a result of the intracellular accumulation of organic osmolytes (slow adaptation). The high osmolality persists despite the normalization of brain volume. Slow correction of the hypertonic state reestablishes normal brain osmolality without inducing cerebral edema, as the dissipation of accumulated electrolytes and organic osmolytes keeps pace with water repletion. In contrast, rapid correction may result in cerebral edema as water uptake by brain cells outpaces the dissipation of accumulated electrolytes and organic osmolytes. Such overly aggressive therapy carries the risk of serious neurologic impairment due to cerebral edema.
by 2.5 mmol per liter \((\frac{77 - 158}{31.5 + 1} = -2.5)\). Since the goal is to reduce the serum sodium concentration by 5 mmol per liter over the next 12 hours, 2 liters of the solution is required \((5 ÷ 2.5)\). With 1 liter added to compensate for ongoing losses of gastric and other fluids, a total of 3 liters will be administered for the next 12 hours, or 250 ml per hour.

After 12 hours, the patient’s serum sodium concentration is 155 mmol per liter. She is febrile and mildly somnolent but hemodynamically stable. Her weight is 64 kg, and the estimated total body water is 32 liters \((0.5 \times 64)\). The physician is dissatisfied with the pace of correction and decides to switch to 0.2 percent sodium chloride, with the goal of reducing the serum sodium concentration by 10 mmol per liter over the next 24 hours. The retention of 1 liter of this solution is estimated to reduce the serum sodium concentration by 3.7 mmol per liter \([(34 - 155) ÷ (32 + 1) = -3.7]\). Thus 2.7 liters of solution is required \((10 ÷ 3.7)\). With the addition of 2 liters to compensate for ongoing water and electrolyte losses, a total of 4.7 liters will be administered for the next 24 hours, or approximately 200 ml per hour.

### Hypotonic Sodium and Potassium Loss

A 62-year-old man with advanced alcoholic cirrhosis is receiving lactulose for the management of hepatic encephalopathy. On examination, confusion, ascites, and asterixis are present. The blood pressure is 105/58 mm Hg while the patient is in the supine position, and the pulse is 110 beats per minute. The serum sodium concentration is 160 mmol per liter, the potassium concentration is 2.6 mmol per liter, and the body weight is 64 kg. The hypernatremia reflects hypotonic sodium and potassium losses induced by lactulose therapy (Fig. 1D). Thus, in addition to the withdrawal of lactulose, 0.2 percent sodium chloride containing 20 mmol of potassium chloride per liter will be administered. With the presence of ascites, the estimated volume of total body water is about 38 liters \((0.6 \times 64)\). Because the serum sodium concentration is determined by the ratio of the “exchangeable” (i.e., osmotically active) portions of the body’s sodium and potassium content to the total volume of body water, the addition of potassium to the infusate requires its inclusion in the calculation of the change in the serum sodium concentration. Formula 2, a simple derivative of formula 1 (Table 2), takes into account the potassium concentration of the infusate. According to this formula, the retention of 1 liter of 0.2 percent sodium chloride containing 20 mmol of potassium chloride will reduce the serum sodium concentration by 2.7 mmol per liter \([(34 + 20) - 160 ÷ (38 + 1) = -2.7]\). To reduce the serum sodium concentration by 10 mmol per liter over the next 24 hours, 3.7 liters of solution \((10 ÷ 2.7)\) is required. With 1.5 liters added to compensate for ongoing obligatory fluid and electrolyte losses, a total of 5.2 liters will be administered over the next 24 hours, or about 220 ml per hour.

Clearly, the use of formula 1 (and its derivative,
sis, hemofiltration, or peritoneal dialysis must be used. The expanded extracellular-fluid volume, hemodialy-
lem. Since diuretics cannot be relied on to reduce volume overload poses a special management prob-
cession.

the patient's clinical status and serum sodium con-
require adjustments based on close monitoring of extracellular-fluid volume calls for great caution in allowing for the fluid losses, but not the sodium and extrarenal hypotonic fluid losses. Although al-
reduction will be counteracted by ongoing renal infusate at a rate of 250 ml per hour. This estimated eight hours, 2.0 liters of 5 percent dextrose will be
concentration by 3.0 mmol per liter ([140 ÷ serum sodium concentration]). Although this formula provides an adequate estimate of the water deficit in patients with hypernatremia caused by pure water loss, it underestimates the deficit in patients with hypotonic fluid loss (Fig. 1). Furthermore, the conventional formula is not useful when sodium and potassium, in addition to water, must be prescribed.8

Hypertonic Sodium Gain

A 60-year-old man has received 10 ampules of sodium bicarbonate over a period of six hours during resuscitation after recurrent cardiac arrest. He is stuporous and is undergoing mechanical ventilation. His blood pressure is 138/86 mm Hg, and peripheral edema (++) is present. The serum sodium concentration is 156 mmol per liter, the body weight is 85 kg, and the urinary output is 30 ml per hour. The hypernatremia is caused by hypertonic sodium gain (Fig. 1E), and its correction requires that the excess sodium and water be excreted. The administration of furosemide alone will not suffice, because furose-
mide-induced diuresis is equivalent to one-half iso-
tonic saline solution; thus, the hypernatremia will be aggravated.10 The administration of both furosemide and electrolyte-free water will meet the therapeutic goal. The estimated volume of total body water is 51 liters (0.6 × 85). The retention of 1 liter of 5 percent dextrose is estimated to decrease the serum sodium concentration by 3.0 mmol per liter ([10−156] ÷ [51+1] = −3). To reduce the serum sodium concentration by 6.0 mmol per liter over a period of eight hours, 2.0 liters of 5 percent dextrose will be infused at a rate of 250 ml per hour. This estimated reduction will be counteracted by ongoing renal and extrarenal hypotonic fluid losses. Although allow-
for the fluid losses, but not the sodium losses, must be considered, the patient’s expanded extracellular-fluid volume calls for great caution in administering fluids. Thus, the fluid prescription will require adjustments based on close monitoring of the patient’s clinical status and serum sodium concentration.

Hypernatremia with concurrent renal failure and volume overload poses a special management problem. Since diuretics cannot be relied on to reduce the expanded extracellular-fluid volume, hemodialysis, hemofiltration, or peritoneal dialysis must be used.

Common Errors in Management

Isotonic saline is unsuitable for correcting hypernatremia. Consider a 50-year-old man with a serum sodium concentration of 162 mmol per liter and a body weight of 70 kg (estimated volume of total body water: 42 liters [0.6 × 70]). The retention of 1 liter of 0.9 percent sodium chloride will decrease the serum sodium concentration by only 0.2 mmol per liter ([154−162] ÷ [42+1] = −0.2). Although the sodium concentration of the infusate is lower than the patient’s serum sodium concentration, it is not suf-
iciently low to alter the hypernatremia substantially. Furthermore, ongoing hypotonic fluid losses might outpace the administration of isotonic saline, aggra-
vating the hypernatremia. The sole indication for ad-
mini-sting isotonic saline to a patient with hyper-
natremia is a depletion of extracellular-fluid volume that is sufficient to cause substantial hemodynamic compromise. Even in this case, after a limited amount of isotonic saline has been administered to stabilize the patient’s circulatory status, a hypotonic fluid (i.e., 0.2 percent or 0.45 percent sodium chloride) should be substituted in order to restore normal hemody-
namic values while correcting the hypernatremia. If a hypotonic fluid is not substituted for isotonic saline, the extracellular-fluid volume may become seriously overloaded.

Extreme care must be taken to avoid excessively rapid correction or overcorrection of hypernatremia, which increases the risk of iatrogenic cerebral edema, with possibly catastrophic consequences. Selecting the most hypotonic infusate that is suitable for the particular type of hypernatremia ensures the admin-
istration of the least amount of fluid. Appropriate al-
allowances for ongoing fluid losses must be made to prevent serious deviations in either direction from the targeted serum sodium concentration. Scrupulous adherance to these management guidelines should help prevent such complications. Most important, the fluid prescription should be reassessed at regular intervals in the light of laboratory values and the patient’s clinical status.

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