Acute Kidney Injury, Sodium Disorders, and Hypercalcemia in the Aging Kidney
Diagnostic and Therapeutic Management Strategies in Emergency Medicine

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KEYWORDS
- Graying of America
- Renal aging
- Hyponatremia
- Hypernatremia
- Hypercalcemia
- Acute kidney injury
- Hypovolemia
- Hyperkalemia

KEY POINTS
- Structural and functional changes make the older patient more susceptible to acute kidney injury (AKI) and fluid and electrolyte disorders.
- When evaluating patients with hyponatremia, it is very important to classify the type of hyponatremia present. This classification is based on the patient’s volume status, serum osmolarity, specific gravity of urine, and sodium concentration.
- Management is based on the type of hyponatremia the patient has and the patient’s clinical status. For patients who have extremely low serum sodium levels and significant neurologic symptoms, such as seizures or altered mental status, treatment with hypertonic saline is the therapy of choice. Also, specific treatment of any underlying disorder should be given.
- Hypernatremia often presents in geriatric patients as dehydration and altered mental status.
- Management of severe hypercalcemia in geriatric patients should consist of hydration with normal saline, intravenous bisphosphonates, and calcitonin and treating the underlying cause.
- Underlying causes of acute renal failure, such as sepsis, hypovolemia, drug toxicity, and urinary obstruction, must be looked for and treated expeditiously.
INTRODUCTION

Improvements in sanitation and health care have led to a worldwide increase in human life expectancies. Simultaneously, lower growth rates in the developed world have contributed to the relative increase in the geriatric population. Thus, by 2030, there will be 71 million Americans aged 65 years or older accounting for approximately 20% of the US population. The “Graying of America” is real and has a real effect on the medical care that is delivered.

An important geriatric medical issue with socioeconomic ramifications is that of renal diseases and electrolyte disorders associated with aging. According to the US Renal Data System, during 1995 to 2005, the adjusted point prevalence rates per million population of reported end-stage renal disease (ESRD) increased from 3627.5 to 5500.6 (51% increase) in the age group of 65 to 74 years and from 2762.4 to 4795.8 (73% increase) in those older than 75 years. This increase seems to be because the management advances for cardiovascular and other diseases have prolonged the lives of older patients and given them the unfortunate opportunity to develop ESRD.

It may also be that new advances in screening for and diagnosing renal disease have increased the numbers of patients who are diagnosed with renal failure at earlier ages.

RENAL AGING

Aging in most species is associated with impaired adaptive and homeostatic mechanisms, leading to susceptibility to environmental or internal stresses that manifest clinically as increasing rates of disease, and the same is true of the kidney. Aging is associated with renal structural changes, functional decline and more difficulty in maintaining electrolyte balance.

STRUCTURAL CHANGES IN THE AGING KIDNEY

Grossly, the renal mass progressively decreases with age because the number and size of the glomeruli decrease with age. The average kidney weight progressively declines after the fifth decade of life, with the renal cortex being affected more than the medulla.

**Vascular Changes**

Arterial sclerosis is the main feature of the aging renal vasculature. The artery walls appear thick, and the vascular lumen is narrowed. This change is due to collagen increase in the media and intimal thickening, which is focal in its distribution, leading to heterogeneous cortical ischemia. None of these vascular changes are pathognomonic for aging and are often associated with several other conditions, including hypertension and diabetes.

The aging kidney also contains a high percentage of afferent and efferent arterioles that communicate directly with each other (“aglomerular arterioles”) because of loss of their glomeruli, particularly in the juxtamedullary location. The aglomerular arterioles cause shunting of blood to the medulla, an increase in filtration fraction in the medulla, and medullary glomerular hypertrophy.

**Glomerular Changes**

Nyengaard and Bendtsen reported changes in glomerular number and size in relation to age. They showed that the number and the size of glomeruli were inversely proportional to age. Moreover, glomerular size was inversely proportional to kidney weight. In addition, the percentage of glomeruli showing global glomerulosclerosis increases.
with age, and there are direct correlations between the number/percentage of globally sclerotic glomeruli and increasing age as well as between the number and percentage of globally sclerotic glomeruli and intrarenal arterial disease, particularly outer cortical arterial disease. Up to 10% of the glomeruli may be globally sclerotic in “normal” subjects younger than 40 years. Smith and colleagues have suggested that beyond 40 years of age the percentage of “aging-related” sclerosed glomeruli is well represented by the formula (patient’s age/2) – 10. Glomerular shape changes as well, with the spherical glomerulus in the fetal kidney developing lobular indentations as it matures. With aging, lobulation tends to diminish and the length of the glomerular tuft perimeter decreases relative to the total area. Both diminished glomerular lobulation and sclerosis of glomeruli tend to reduce the surface area available for filtration and therefore contribute to the observed age-related decline in glomerular filtration rate (GFR).

**Tubulointerstitial Changes**

Renal tubules undergo fatty degeneration and irregular thickening of their basal membrane with increasing zones of tubular atrophy and fibrosis. The distal renal tubules develop diverticula that increase in number with advancing age. The diverticula in distal and collecting tubules may be precursors of the simple renal cysts that are seen in half of the subjects older than 40 years. The number of renal cysts is greater in older patients than in younger patients. These cysts may cause complications such as rupture, infection, and obstruction. In addition, the aging human kidney is associated with mesangial matrix expansion and thickening of the glomerular basement membrane.

**FUNCTIONAL CHANGES IN THE AGING KIDNEY**

**Renal Hemodynamics**

In 1940, Goldring and colleagues reported a progressive decline of renal plasma flow (RPF) with aging in humans. Shock and colleagues demonstrated a decreased clearance of $\text{p}$-aminohippurate in the older population, with the clearance decreasing from 600 mL/min per 1.73 m$^2$ in young adults to almost 300 mL/min per 1.73 m$^2$ by the age of 80 years. The RPF is maintained through the fourth decade and then declines at the rate of 10% per decade. The reduction in RPF is not entirely due to loss of renal mass, as xenon washout studies demonstrate a progressive reduction in blood flow per unit kidney mass with advancing age. The decrease in RPF is most profound in the renal cortex; redistribution of flow from cortex to medulla may explain the slight increase in filtration fraction seen in older patients. Under normal conditions, the renal function reserve is the significant increase in the renal blood flow and GFR in response to renal vasodilation. The increase in RPF and GFR in response to maximum renal vasodilation induced by concurrent infusion of amino acids and dopamine is markedly reduced in healthy older individuals; this age-related impairment in renal hemodynamics is mainly because of morphologic changes, more specifically age-related renal vascular changes, rather than functional changes. The reduction in renal hemodynamic and functional reserves can compromise renal adaptation to acute ischemia and as such can heighten susceptibility to acute renal injury in the geriatric population.

**Glomerular Function**

GFR is low at birth, approaches adult levels by the end of the second year of life, and is maintained at approximately 140 mL/min/1.73 m$^2$ until the fourth decade. As indicated
by the classical inulin test, GFR declines by about 8 mL/min/1.73 m² per decade thereafter.18–24 Several studies have reported a decrease in GFR with age, with a delayed and slower decrease in women compared with men.21–25

In clinical practice, creatinine clearance is estimated in older patients using either the Cockcroft–Gault (CG) equation or the MDRD (modification of diet in renal disease) formula.26 Creatinine clearance is influenced by the nutritional status, protein intake, and muscle mass and is therefore not an accurate measure of the GFR in geriatric patients.27 A study showed more than 60% discordance in GFR estimation by the 2 equations in individuals older than 65 years. The MDRD equation generally yielded higher estimates of GFR than the CG equation.28 This observation has important implications, especially when calculating drug dosages in older patients. Overestimation of GFR can inadvertently result in unexpected drug toxicity. It was thus recommended that the CG equation should be used in preference to the MDRD equation to estimate GFR for drug dosage calculations in geriatric patients.29

**Sodium Balance**

The time required for the decrease in urinary sodium excretion in response to dietary sodium chloride deprivation is significantly prolonged in healthy older individuals when compared with young individuals.30 The aging kidney also demonstrates an impaired capacity to respond to a sodium load. As shown by Luft and colleagues,31 after a load of a 2-L saline infusion, older subjects excreted only $310 \pm 9$ mEq/24 h as opposed to $344 \pm 5$ mEq/24 h in subjects younger than 40 years. Furthermore, in older patients, the levels of plasma renin activity and serum aldosterone are reduced, and this could reduce the capacity of the kidney to retain sodium even more.32 The critical effect of impaired sodium conservation in geriatric patients is that a 2-L diuresis induces a 24-mm Hg drop of systolic blood pressure in older subjects but not in young adults.33 Therefore, the impaired ability to retain sodium may predispose geriatric patients to hemodynamic instability.

**Potassium Balance**

The excretion of potassium is derived from active transtubular transport in the distal nephron and collecting duct, which is linked to the reabsorption of sodium across the aldosterone-mediated Na-K ATPase transporters. Thus, impaired potassium secretion (and the corresponding impaired sodium reabsorption) may occur because of structural changes such as tubular atrophy, tubulointerstitial scarring due to ongoing glomerulosclerosis, or low levels of renin or aldosterone.34 Furthermore, the prevalence of sodium and potassium disturbances increases with age and is associated with medication use.35 Other studies in experimental animals have demonstrated that aging is characterized by impairment of the ability of renal tubules to adapt to a high potassium intake. This reduced efficiency of renal potassium excretion is associated with extrarenal impairment in potassium excretion, probably caused by a reduced activity of colon Na-K ATPase transporter.36 These changes make older patients more likely to develop hyperkalemia, especially when given potassium supplements, potassium-sparing drugs such as spironolactone, or drugs that affect the renin-aldosterone system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

**Renal Concentration and Dilution**

Several studies have demonstrated an impaired renal concentrating ability in geriatric patients.37,38 Studies in experimental animals have also demonstrated decreased responsiveness of renal tubules to arginine vasopressin (AVP), caused by a decrease...
in cyclic adenosine monophosphate generation and a lower expression of aquaporin-2 (AQP2).\textsuperscript{39,40} These changes in renal concentration ability lead to hypernatremic dehydration in older patients. In addition, the renal diluting ability is also impaired in older subjects. In fact, after a water load, older subjects failed to reach the urine osmolality shown by younger subjects.\textsuperscript{41} This impairment predisposes geriatric patients to hyponatremia, if excess fluid is administered.\textsuperscript{42}

**Other Physiologic Changes**

Frassetto and colleagues\textsuperscript{43} demonstrated that there is a progressive decline in plasma bicarbonate, with development of a moderate acidosis, in healthy older subjects with a steady state acid diet. The impairment of acid excretion may be due to a decrease in renal mass\textsuperscript{44} or a reduction in ammonia production secondary to intrinsic tubular defect.\textsuperscript{45} These changes make the older patient more likely to develop a metabolic acidosis, which can be a high anion gap and/or a normal anion gap acidosis. This acidosis can also cause hyperkalemia in these older patients.

In healthy subjects, the serum erythropoietin levels increase with increasing age.\textsuperscript{46} However, the levels are unexpectedly lower in older anemic patients than in younger anemic patients, suggesting a blunted response to low hemoglobin levels.\textsuperscript{47,48} Thus, it is more difficult for older patients to compensate for anemia and to respond to treatment of anemia.

**HYPONATREMIA**

**Epidemiology**

Hyponatremia, commonly defined as a serum sodium concentration less than 136 mEq/L (1 mEq/L = 1 mmol/L), is among the most common electrolyte abnormalities encountered in clinical practice.\textsuperscript{49} In addition, patients with hyponatremia have a significantly increased risk of death during hospitalization and at 1 year and 5 years after admission.\textsuperscript{50} However, in the emergency department (ED) study by Vroonhof and colleagues,\textsuperscript{51} in patients visiting the ED, irrespective of the underlying condition, hyponatremia was not associated with an increase in mortality. As mentioned previously, the age-related changes and the effect of chronic diseases in the sensation of thirst, renal function, concentrating abilities, and hormonal modulators of sodium and water balance make geriatric patients more susceptible to impairment of water metabolism, which increases the risk of dehydration. Information on the frequency of hyponatremia in the ED setting is scarce. One study, reported by Lee and coworkers\textsuperscript{52} observed a 4% prevalence of hyponatremia (serum sodium levels <134 mEq/L) in an adult internal medicine patient population treated in the ED. Hypovolemic hyponatremia represents 65% of these cases, with the most common underlying disorders being those of the gastrointestinal system.\textsuperscript{52} After adjusting for gender, increasing age (>30 years old) was independently associated with both hyponatremia at presentation and hospital-acquired hyponatremia (serum sodium levels <136 mEq/L) (Fig. 1).\textsuperscript{53}

In a study comparing the prevalence of hyponatremia in patients in nursing home with ambulatory geriatric patients, aged 60 years or older, the most recent serum sodium levels identified 18% of patients in the nursing home to be hyponatremic, compared with a prevalence of 8% in similarly aged ambulatory patients. In the nursing home population, 53% of the patients had at least 1 episode of hyponatremia in the previous 12 months. There was a high incidence of central nervous system (CNS) and spinal cord disease in the patients in the nursing home. Many episodes of hyponatremia were frequently associated with an increased intake of fluids, given either orally or intravenously or with tube feedings.\textsuperscript{54}
There are several risk factors for hyponatremia in the elderly. In a small sample of hospitalized Bronx adults, Choudhury and colleagues identified some of the independent risk factors for hyponatremia at admission. Nursing home residents were 43-fold more likely to be hospitalized with hyponatremia (Na levels <135 mEq/L) and 16-fold more likely to be admitted with serum Na levels less than 125 mEq/L than were community patients. In addition, a declining serum Na level during hospitalization increased the risk of adverse outcome by fourfold. The drop in serum sodium levels during admission was strongly associated with increased length of stay, and this had been previously demonstrated by a cohort study in older patients admitted to 2 acute geriatric wards.

Hyponatremia also increases the risk of large-bone (hip, pelvis, or femur) fractures in geriatric patients. Sandhu demonstrated that the incidence of hyponatremia in geriatric patients with fractures was more than double that of nonfracture patients. The degree of hyponatremia was noted to be mild to moderate. In the fracture group, 24.2% were taking antidepressants (3/4 of which were selective serotonin receptor inhibitors [SSRIs]), whereas there was no one taking these medications in the nonfracture group. This result may indicate that administration of antidepressants is a probable risk factor for hyponatremia in geriatric patients. Increased fracture risk in hyponatremia also was independent of recent falls, pointing toward a possible adverse effect of hyponatremia on bone quality.

**Pathophysiology**

Water homeostasis depends on an interaction between specialized sensors that translate the signals they receive (high serum osmolality, low effective circulating volume) to the central release of AVP (the antidiuretic hormone) into the circulation,
which then stimulates water reabsorption in the renal collecting duct. Water balance regulation is primarily designed to maintain serum osmolality between 275 and 290 mOsm/kg and to a lesser extent, the blood volume (vasopressin levels start to increase after a 1% increment in serum osmolality vs a 5%–10% decrease in blood volume). The serum osmolality is sensed by osmoreceptors in several parts of the brain, which stimulate the secretion of vasopressin into the bloodstream. On the other hand, the carotid sinus baroreceptors sense a low effective circulating volume, and parasympathetic afferents transfer this signal to the vasomotor center, which increases the rate of vasopressin secretion by the cells in the paraventricular nuclei. Vasopressin stimulates an intracellular cascade in the renal tubular cells, which ultimately results in the insertion of AQP2 water channels in the apical membrane, which promotes water reabsorption. The thirst stimulus (hypertonicity, hypovolemia, and other hormonal signals [eg, relaxin]) provides another crucial, but less-sensitive, means for the body to maintain water homeostasis by promoting oral intake of free water. Thirst is decreased in older people as evidenced by response to water deprivation. Older persons, when compared with younger people, ingest smaller amounts of water during 24 hours of water deprivation. A similar observation was made when older and younger persons were given hypertonic saline to induce hypertonicity. Older persons drank less water, when compared with their younger counterparts, after being given hypertonic saline.

Dysregulation of AVP can be caused by both osmotic and nonosmotic mechanisms. Although osmotic regulation of AVP is more sensitive, nonosmotic stimulation is more potent. The presence of hyponatremia nearly always implies that vasopressin is released nonosmotically. Anderson and colleagues showed that nonosmotic vasopressin secretion was present in 97% of hyponatremic patients studied. There are 4 mechanisms that result in abnormal vasopressin secretion during hyponatremia:

1. Nonosmotic vasopressin release caused by low effective circulating volume, several diseases, drugs, and nonspecific stimuli, such as anxiety, stress, pain, and nausea.
2. Ectopic vasopressin production (eg, small cell lung cancer).
3. Factors that may enhance the renal effects of vasopressin (eg, cyclophosphamide).
4. A vasopressin-like effect caused by an activating mutation of the vasopressin-2 receptor.

There is increasing evidence for a relationship between high interleukin-6 levels and vasopressin release. Furthermore, recently, a direct relationship was found between an increase in C-reactive protein levels and the development of hyponatremia, suggesting that the acute-phase response, perhaps mediated by interleukin-6, could explain the established relationship between certain infections and hyponatremia.

Clinical Presentation

The signs and symptoms of hyponatremia depend not only on the absolute serum sodium level but also on the rate of serum sodium level decline. The symptoms are nonspecific and are related primarily to its effects on the CNS (Fig. 2). Mild hyponatremia (serum Na levels of 130–134 mmol/L) causes anorexia, cramping, nausea, vomiting, headache, and irritability. Moderate hyponatremia (serum Na levels of 125–129 mmol/L) causes disorientation, confusion, weakness, and lethargy. Acute severe hyponatremia is defined as the development of symptomatic hyponatremia of 125 mmol/L or less within 48 hours and can lead to seizures, coma, permanent brain damage, respiratory arrest, brainstem herniation, and death.
In chronic hyponatremia, symptoms are usually lacking, because of the adaptive mechanism of the brain in patients with sodium levels greater than 125 mEq/L, but when present, they may include subtle defects in gait and cognition. Once serum sodium levels decrease below 125 mEq/L, neurologic symptoms become more profound and may include fatigue, memory impairment, vomiting, nausea, confusion, and seizures. A careful review of recent events, medical history, medication changes, and social and psychiatric history is essential in ascertaining the cause of hyponatremia. Physical examination should be focused on the assessment of the patient’s neurologic status, including the level of consciousness, mental status assessed with the Mini-Mental Status Examination (MMSE), and volume status. In a study, geriatric patients with mild-to-moderate hyponatremia had significantly worse results in MMSE and other standardized tests of geriatric assessment compared with a normonatremic control group. Major clinical indicators of hypervolemia include edema, rales, distended neck veins, and a third heart sound. The major clinical indicators of severe hypovolemia due to blood loss or severe dehydration include postural tachycardia, and severe postural dizziness. In patients with vomiting, diarrhea, or decreased oral intake, the presence of a dry axilla supports the diagnosis of hypovolemia (positive likelihood ratio of 2.8). The hemodynamic response to extracellular fluid volume depletion seems to be dependent on the rate, magnitude, and source of fluid volume loss. Therefore, clinical assessment of the extracellular fluid volume frequently yields misleading results in hyponatremic disorders. Chung and colleagues demonstrated that clinical assessment correctly identified only 47% of hypovolemic patients with hyponatremia. Although the extracellular fluid volume should be routinely assessed in hyponatremic patients, it should be taken into consideration that misjudgment is common.

Tables 1 and 2 suggest some historical elements and some laboratory tests to help with the approach to hyponatremia.

Approach, Classification, and Causes

In the past, hyponatremia would always be classified initially based on the volume status. We find the following approach, which combines the volume status of the

Fig. 2. Effects of transcellular fluid shifts on brain cells in hyponatremia and hypernatremia. Electrolytes and osmolytes shift in response to a hyposmolar and hyperosmolar extracellular environment, respectively, to preserve normal cellular volume. Overly aggressive fluid resuscitation can result in complications, such as osmotic demyelination syndrome and cerebral edema. (From Lin M, Liu SJ, Lim IT. Disorders of water imbalance. Emerg Med Clin North Am 2005;23:749–70; with permission.)
The initial approach to the hyponatremic patient is to measure the serum osmolality or calculate it with the following formula:

\[
\text{Plasma osmolality} = \left( 2 \times \text{Na (mEq/L)} + \frac{\text{Glucose(mg/dL)}}{18} + \frac{\text{BUN(mg/dL)}}{2.8} \right)
\]

where BUN denotes the blood urea nitrogen.

Although urea contributes to the absolute value of serum osmolality measured with an osmometer, it does not hold water within the extracellular space because of its membrane permeability. Urea is an ineffective osmole and does not contribute to

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
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<tbody>
<tr>
<td>Current hospitalization</td>
<td>Recent surgery/trauma/pain</td>
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<td></td>
<td>IVF (hypotonic fluids)</td>
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<td></td>
<td>Irrigation with glycerine (TURP, laparoscopy)</td>
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<tr>
<td>Medical history</td>
<td>Recent vomiting, diarrhea</td>
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<td>Diabetes mellitus, hyperglycemia</td>
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<td></td>
<td>Heart failure, edema, dyspnea</td>
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<td>Pulmonary disease or symptoms</td>
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<td></td>
<td>Renal disease</td>
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<td>Cirrhosis</td>
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<td>Hypothyroidism</td>
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<td>Adrenal insufficiency</td>
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<td>CNS disease or insult</td>
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<td>Medicines</td>
<td>Medication changes</td>
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<td>Diuretics</td>
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<td>ACE inhibitors</td>
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<td></td>
<td>Medications associated with SIAD</td>
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<tr>
<td>Social history</td>
<td>Alcohol (beer potomania)</td>
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<tr>
<td></td>
<td>Dietary history (Tea and toast diet)</td>
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<tr>
<td>Psychiatric history</td>
<td>Psychogenic polydipsia</td>
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### Table 2

<table>
<thead>
<tr>
<th>Laboratory tests to help with the approach to hyponatremia</th>
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<tr>
<td><strong>Initial test</strong></td>
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<tr>
<td>Serum electrolytes</td>
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<tr>
<td>Serum glucose, urea, creatinine, total protein</td>
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<tr>
<td>Serum osmolality</td>
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<tr>
<td>Urine osmolality and urine specific gravity</td>
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<tr>
<td>Urine sodium and creatinine</td>
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<tr>
<td>Calculation of FENa</td>
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<tr>
<td><strong>Additional test</strong></td>
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<tr>
<td>TSH</td>
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<tr>
<td>Morning cortisol level</td>
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<tr>
<td>Serum and urine uric acid</td>
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<tr>
<td>Calculate FEurate</td>
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</tbody>
</table>

**Abbreviations:** ACE, angiotensin-converting enzyme; IVF, intravenous fluids; SIAD, syndrome of inappropriate antidiuresis; TURP, transurethral resection of the prostate.

**Data from Sra J, Repp AB. Hyponatremia. Hosp Med Clin 2012;1:2.**
the effective serum osmolality (tonicity). Based on effective serum tonicity (serum osmolality minus serum urea level), hyponatremia can be classified as hypertonic, isotonic, or hypotonic.

**Hypertonic hyponatremia**
Hyponatremia, with plasma osmolality exceeding 290 mOsm/kg (i.e., hypertonic or hyperosmolar hyponatremia), suggests factitious hyponatremia secondary to hyperglycemia or administration of other osmotically active substances, such as mannitol.75 Hyperglycemia generates a 1.6 to 2.4 mEq/L apparent decrease in plasma sodium for each 100-mg/dL increase in plasma glucose levels above 150 mg/dL.76 Hillier and colleagues77 have proposed that a correction factor of 2.4 mmol/L is a better overall estimate of the association between sodium and glucose levels.

**Isotonic hyponatremia (pseudohyponatremia)**
Hyponatremia with a normal plasma osmolality (275–290 mOsm/kg) is usually seen in patients with severe hypertriglyceridemia or paraproteinemia with serum lipids or protein level greater than 10 g/dL. Many laboratories now measure plasma sodium levels directly using ion-specific electrodes, thus eliminating this artifact.78 The 2 classifications mentioned above should be ruled out (by measuring the serum osmolality, lipid level, and protein level and managing accordingly) before treating hyponatremia.

**Hypotonic hyponatremia**
Most cases of hyponatremia are associated with a low osmolality (<275 mOsm/kg), reflecting a net gain of free water. The next step is measuring urine osmolality or specific gravity.79 If the urine osmolality is less than 100 mOsm/kg, or if the specific gravity is 1.003 or less, then the urine is maximally dilute, which indicates that vasopressin secretion is completely and appropriately suppressed. This finding of hyponatremia and hyposmolar urine (<100 mOsm/kg) is seen in primary polydipsia or reset osmostat syndrome and is also observed in cases of extremely reduced solute intake as in “beer potomania syndrome.”

**Hyponatremia with hyposmolar urine (<100 mOsm/kg)**
Psychogenic polydipsia (primary polydipsia) occurs most frequently among schizophrenic patients and is characterized by excessive water intake, often in excess of 10 L/d.80 Typical antipsychotics have been reported to worsen the polydipsia, favoring the use of atypical antipsychotics in these patients.81 Beer potomania is a rare cause of severe hyponatremia, and it is associated with a high rate of mortality and the osmotic demyelination syndrome (ODS).82 The diagnosis is made based on the clinical history of heavy alcohol consumption in the setting of an otherwise poor nutritional intake and recognition of the low urine osmolality. Treatment of patients with beer potomania with isotonic or hypertonic saline causes brisk free-water diuresis, thereby increasing the risk of overly rapid sodium correction and ensuing osmotic demyelination. When serum sodium levels increase faster than 10 mEq/L in 24 hours or 18 mEq/L in 48 hours, dextrose 5% in water (D5W) should be infused at a rate to match the urine output (UO), and if needed, desmopressin may be used.82,83 Reset osmostat syndrome is a subset of the syndrome of inappropriate antidiuresis (SIAD) (formerly called syndrome of inappropriate antidiuretic hormone [SIADH]), which is often seen in elderly patients with pulmonary disease (e.g., tuberculosis), and malnutrition.84 When necessary, a water-loading test can be performed to distinguish reset osmostat syndrome from other patterns of AVP release.85 When hyponatremia occurs because of “reset osmostat,” renal concentrating and diluting...
capacities are normal but the regulation of AVP to maintain serum tonicity takes place at a lower osmolal threshold.

**Hyponatremia with urine osmolality greater than 100 mOsm/kg** If the urine osmolality is greater than 100 mOsm/kg, vasopressin-dependent impaired water excretion is indicated. The next step is to determine the urine sodium concentration, fractional excretion of sodium (FENa), and volume status. Urine sodium concentration less than 20mEq/L (ie, sodium conservation), and in older patients, levels of up to 30 mEq/L, are considered to indicate some degree of conservation of sodium.30

When the urine Na level is less than 30, the next step is to measure the volume status, which will be either hypovolemic or hypervolemic.

**Hypovolemic hyponatremia with urine Na levels less than 30 mEq/L** Hypovolemia with urine sodium levels less than 30 mEq/L or FENa less than 1% suggests active renal sodium retention to compensate for extrarenal losses that occur with gastrointestinal disorders with volume losses, due to vomiting, diarrhea, or third spacing; severe burns; or insensible losses. These patients represent the most common cause of hyponatremia found in patients in the ED (about 24.1%).52 These patients need replacement of both volume and sodium.

**Hypervolemic hyponatremia with urine Na levels less than 30 mEq/L** Hyponatremia in the setting of an increased total body water (TBW) volume occurs in edematous states, such as congestive heart failure, liver failure, and nephrotic syndrome associated with a low effective arterial blood volume.86 As a response to the reduced baroreceptor activity, the renin-angiotensin system is activated first, whereas the vasopressin axis is activated after a greater decrease in arterial filling. Recently, hyponatremia was also found to be a predictor of long-term mortality and admission for heart failure after hospital discharge in survivors of acute ST elevation myocardial infarction.87

A urine Na level greater than 30 mEq/L indicates that there is some sodium wasting, and the next step is to measure the volume status.

**Hypovolemic hyponatremia with urine Na levels greater than 30 mEq/L** This condition is seen in diuretics-induced hyponatremia. Although loop diuretics are more potent than thiazide diuretics, the latter are much more likely to cause hyponatremia. In cases of diuretic-induced hyponatremia, 73% was caused by thiazide diuretics alone, 20% by thiazide diuretics in combination with antikaliuretic agents, and only 8% was due to furosemide alone.88 Thiazide-induced hyponatremia occurs most commonly in elderly women.

Other cause of hypovolemic hyponatremia with urine Na levels greater than 30 mEq/L are salt-losing nephropathies, including renal tubular acidosis, polycystic kidney disease, and obstructive uropathy. Both type II renal tubular acidosis and metabolic alkalosis cause hyponatremia as a result of bicarbonaturia, which obligates sodium excretion.

Cerebral salt wasting syndrome (CSWS) has been described in patients with intracranial disease (mainly those with subarachnoid hemorrhage).89 Although the exact mechanism of natriuresis is unknown, it has been suggested that a brain natriuretic peptide is released and causes an increase in sodium excretion and urine volume.89

Volume status is a distinguishing feature, with euvolemia associated with SIADH and hypovolemia associated with CSWS. However, accurate determination of volume status under these conditions can be difficult.90 Interestingly, the fractional excretion of urate (FEurate) has been reported as a means of distinguishing these syndromes. In both SIADH and CSWS, FEurate may increase more than 10%, but correction of
Hyponatremia normalizes FE\textsubscript{urate} to less than 10% in SIADH, but not in CSWS.\textsuperscript{91} Moreover, random urine sodium concentrations tend to exceed 100 mEq/L in CSWS, but rarely, if ever, in SIADH.

**Euvolemic hyponatremia with urine Na levels greater than 20 mEq/L** Hypothyroidism is a rare cause of euvolemic hypotonic hyponatremia that sometimes manifests as severe hyponatremia, and although the underlying mechanism is unclear, inappropriately elevated levels of circulating AVP is thought to be the cause of fluid retention.\textsuperscript{92} Another endocrine disorder associated with hyponatremia is primary adrenal insufficiency, which is often missed, possibly because hyperkalemia is absent in one-third of the cases.\textsuperscript{93} Hypopituitarism with secondary adrenal insufficiency is another overlooked cause of hyponatremia\textsuperscript{94} and might be differentiated from SIAD by the presence of a compensated respiratory alkalosis with low plasma bicarbonate and low carbon dioxide levels.\textsuperscript{95}

SIAD is a new terminology that is currently used, and it is a more generalized term than SIADH. In patients with euvolemic hyponatremia, several other clinical entities need to be excluded before making the diagnosis of SIAD. These include hypothyroidism, adrenal insufficiency, and hypopituitarism. There are specific criteria for diagnosis of SIAD. To be diagnosed with SIAD, patients must be euvolemic, have a urine osmolality greater than 100 mOsm/kg, and have a low effective plasma osmolality. Moreover, excessive water intake is necessary for hyponatremia to develop.\textsuperscript{96} There are 4 patterns of SIAD. These patterns are unregulated vasopressin secretion, elevated basal secretion of vasopressin despite normal regulation by osmolality, a reset osmostat syndrome, and nephrogenic SIAD,\textsuperscript{97} which is characterized by undetectable vasopressin levels, unresponsiveness to vasopressin-receptor antagonists, and an abnormal response to a water-loading test. The causes of SIAD are myriad, and they are best classified into pulmonary disorders, malignant diseases, disorders of the nervous system, and drug-induced SIAD (Table 3). SSRI use poses a risk of development of hyponatremia, especially in patients who are older and have smaller body size.\textsuperscript{98} Aging may be a risk factor for the development of SIAD-like hyponatremia in a subset of older patients who do not have an apparent underlying cause.\textsuperscript{99} Patients with SIAD commonly exhibit low serum uric acid levels (<0.24 mmol/L), and it is associated with increased fractional excretion of urate (>10%).\textsuperscript{100} Fig. 3 shows an algorithm that can be used to differentiate the different causes of hyponatremia in older patients.

**Management**

Plasma osmolality provides the basis for an initial approach to management of hyponatremia. In hypertonic hyponatremia, treatment is directed at the underlying cause, for example, treating the hyperglycemia with fluids and insulin. No specific treatment is indicated for isotonic hyponatremia (ie, pseudohyponatremia) other than treating the underlying lipid disorder and investigating the protein disorder. Treatment of hypotonic hyponatremia is guided foremost by the presence or absence of symptoms and then by clinical volume status. Acute hyponatremia (occurring in <48 hours and more likely to be symptomatic) should be treated rapidly to prevent cerebral edema, whereas chronic hyponatremia (defined as present more than 48 hours) should be treated slowly to avoid OSD.\textsuperscript{72} When the patient is severely symptomatic, for example, having seizures, severe altered mental status, or coma, aggressive therapy should be initiated. The treatment of choice is 3% hypertonic saline at 100 mL/h. For each 100 mL of 3% hypertonic saline, the serum sodium concentration increases by approximately 2 mmol/L. Hypertonic saline should not be used before laboratory
<table>
<thead>
<tr>
<th>Central Nervous System Disorders</th>
<th>Neoplasms with Ectopic ADH Production</th>
<th>Pulmonary Disease</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular diseases (thrombosis, embolism, hemorrhage, vasculitis)</td>
<td>Small cell carcinoma of the lung</td>
<td>Pneumonia</td>
<td>CNS active drugs</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>Trauma (subdural hematoma, subarachnoid or intracranial hemorrhage)</td>
<td>Pharyngeal carcinoma</td>
<td>Lung abscess</td>
<td>Antipsychotics</td>
<td>AIDS</td>
</tr>
<tr>
<td>Tumor</td>
<td>Pancreatic carcinoma</td>
<td>Bronchiectasis</td>
<td>Antidepressants (tricyclics, selective serotonin reuptake inhibitors)</td>
<td>Idiopathic SIAD of the elderly</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Thymoma</td>
<td>Tuberculosis</td>
<td>Anticonvulsants (carbamazepine)</td>
<td></td>
</tr>
<tr>
<td>Infection (meningitis, encephalitis, brain abscess)</td>
<td>Lymphoma, Hodgkin disease, reticulum cell sarcoma</td>
<td></td>
<td>Narcotics</td>
<td></td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Bladder carcinoma</td>
<td></td>
<td>Hallucinogens (Ecstasy)</td>
<td></td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td></td>
<td></td>
<td>ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>Postoperative trans-sphenoidal hypophysectomy</td>
<td></td>
<td></td>
<td>Antineoplastic agents (vincristine, vinblastine, cyclophosphamide)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td>Oxytocin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ADH analogs (desmopressin, lysine vasopressin)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sulfonyleureas (chlorpropamide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypolipidemics (clofibrate)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ACE, angiotensin-converting enzyme; ADH, antidiuretic hormone; AIDS, acquired immune deficiency syndrome.*

confirmation of hyponatremia and should be used only in a closely monitored setting (ie, intensive care unit [ICU] or ED).\textsuperscript{101} Duration of the hypertonic saline infusion is guided by the improvement of the patient’s symptoms, or when the serum Na level reaches 120 mEq/L. The correction rate of acute hyponatremia should not exceed 8 to 10 mmol/L for the first 24 hours and 18 to 25 mmol/L for the first 48 hours.\textsuperscript{101} In chronic hyponatremia, the correction goal is 6 mEq/L during the initial 24 hours.\textsuperscript{102} The Adrogue–Madias formula\textsuperscript{73} is the most widely used formula to predict the increment in serum sodium concentration after the infusion of either isotonic saline or hypertonic saline.\textsuperscript{73} The use of this formula is demonstrated in Table 4.

For example, in a 80-kg elderly man who presents with significant altered mental status and a sodium concentration of 103 mEq/L, hypertonic saline should be instituted immediately in the ED. It is observed that 1 L of 3\% saline (513 mEq/L sodium)
increases the serum sodium concentration by approximately 10 mEq/L, as calculated by 
\[ \frac{(513 - 103)}{(0.5 \times 80) + 1} \]. Thus, to increase the serum sodium concentration by 2 
mEq/L in the first hour, one-fifth of a liter (200 mL) should be given.

The cornerstone of treatment of hypovolemic hypotonic hyponatremic patients is 
volume replacement with normal saline solutions. The elderly patient’s vital signs 
and state of hydration (oxygen saturation by pulse oximeter, respiratory rate, and 
breath sounds) should be carefully monitored to ensure that the patient receives 
adequate volume replacement but does not become fluid overloaded. Also, any 
underlying cause of the patient’s volume loss should be treated.

In asymptomatic patients with euvoicmic (eg, SIAD) or hypervolemic hyponatremia 
(eg, cirrhosis with ascites and edema), fluid restriction is generally the treatment of 
choice. There are now nonpeptide antagonists to V2 vasopressin receptors, 
commonly referred to as “vaptans” or “aquaretics,” which increase free water excre-
tion and serum sodium concentration. One of these agents is conivaptan, which has 
been approved by the US Food and Drug Administration for intravenous use in the 
hospital to treat euvoicmic and hypervolemic hyponatremia, specifically that due to 
SIAD and congestive heart failure (CHF).101

Treatment of SIAD can range from free-water restriction in asymptomatic patients to 
isotonic or hypertonic saline infusion in severely symptomatic patients. Hospitalized 
patients with symptomatic SIAD who do not respond to these treatments or who 
will not adhere to water restriction can be treated with either democycline or conivap-
tan. The dose of demeclocycline is 300–600 mg orally twice a day. It has an onset of 
action of 5–14 days. Conivaptan is administered as a loading dose of 20 mg intrave-
nously, followed by a continuous intravenous infusion of 20–40 mg a day for no more 
than 4 days.103 Corticosteroids can be used if hypocortisolism is suspected, and flu-
drocortisone can be used if hyponatremia is due to CSWS.104

In addition to directly treating the hyponatremia, it is very important to treat any 
underlying diseases that are causing or contributing to the hyponatremia, such as 
gastrointestinal, neurologic, cardiac, renal, pulmonary, psychiatric, and endocrine 
disorders. It is also very important to stop any medication that could be causing or 
aggravating the hyponatremia.

**Osmotic demyelination syndrome**

Osmotic demyelination syndrome is a well-recognized clinical entity and is a dreadful 
complication that classically occurs several days after aggressive rapid therapy for

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**Table 4**

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Change in plasma sodium = ((\text{Infusate sodium} - \text{plasma sodium})/ (\text{Total body water} + 1))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Body Water = Weight(kg) × Correction Factor</strong></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Correction Factor</td>
</tr>
<tr>
<td>Male, elderly</td>
<td>0.5</td>
</tr>
<tr>
<td>Female, elderly</td>
<td>0.45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Na on the Infusate Solution</strong></th>
<th><strong>IV Fluid</strong></th>
<th><strong>Na (mEq/L)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>D5W</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.2% saline</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>0.45% saline</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>0.9% saline</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>3% saline</td>
<td>513</td>
<td></td>
</tr>
</tbody>
</table>
chronic hyponatremia. Osmotic demyelination syndrome includes central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM). CPM and EPM are the same disease, sharing the same conditions, associations, and time course but differing in clinical manifestations. Different areas of the brain can be involved (Box 1).

The brain adaptation mechanism to hyponatremia begins shortly after an acute fall in serum sodium levels and is complete within 2 days. It is characterized initially by the loss of interstitial sodium and water into the cerebrospinal fluid because of increased hydraulic pressure and, within hours, by the loss of intracellular potassium, sodium, and organic solutes, called osmolytes (such as myoinositol, glutamate, and glutamine), from brain cells. This mechanism provides protection against cerebral edema. In chronic hyponatremia, this brain adaptation is already established, and these solutes cannot be as quickly replaced when the brain volume begins to shrink in response to correction of the hyponatremia. As a result, brain volume decreases from a value that is initially somewhat above normal to one below normal with rapid correction of hyponatremia, resulting in demyelination of areas of the brain. In contrast, overly rapid correction is not likely to induce ODS in patients with acute severe hyponatremia that has only been present for several hours, because the cerebral adaptation is at an early stage. The process by which demyelination occurs is not completely understood. Box 2 lists some of the risk factors for OSD.

The clinical features vary according to the site of involvement in the brain. The initial signs of CPM include dysarthria and dysphagia (secondary to corticobulbar fiber

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**Box 1**

**Areas of the brain that can be involved in CPM and EPM in descending order of frequency**

- Pons
- Cerebellum
- Lateral geniculate body
- External capsule
- Extreme capsule
- Hippocampus
- Putamen
- Cerebral cortex/subcortex
- Thalamus
- Caudate nucleus

_The following areas are involved in 10% or less cases:_

- Claustrum
- Internal capsule
- Midbrain
- Internal medullary lamella
- Mamillary body
- Medulla oblongata

involvement) and a flaccid quadriparesis (from corticospinal tract involvement), which later becomes spastic, and all these are due to involvement of the base of the pons. If the lesion extends into the tegmentum of the pons, then pupillary and oculomotor abnormalities may occur. EPM is characterized by tremor and ataxia. In extreme cases, a “locked-in syndrome” may be present.\textsuperscript{105} OSD can be seen on computed tomography (CT) or magnetic resonance imaging (MRI). MRI findings tend to lag behind the clinical features in some cases as much as by 1 to 2 weeks,\textsuperscript{107} and if this diagnosis remains likely, a repeat imaging study at 10 to 14 days may reveal lesions not apparent on early scans. The management of patients with ODS is prolonged neurorehabilitation. There are case series about use of intravenous immunoglobulin\textsuperscript{108} and reinduction of hyponatremia\textsuperscript{109} with good outcomes. The prognosis is very difficult to be predicted. The outcome may be death, disability, or recovery.

Summary
Hyponatremia is more common in the older patients, because of the decreased ability and reserve to maintain homeostasis of fluids and electrolytes and the presence of more comorbidities.

Severe hyponatremia in geriatric patients has significant morbidity and mortality, because of neurologic complications, such as altered mental status, seizures, and coma.

When evaluating patients with hyponatremia, it is very important to classify what type of hyponatremia is present. Classification is based on the patient’s volume status, serum osmolarity, specific gravity of urine, and sodium concentration.

Management is based on the type of hyponatremia the patient has and the patient’s clinical status. For patients who have extremely low serum sodium levels and significant neurologic symptoms, such as seizures or altered mental status, treatment with hypertonic saline is the therapy of choice. Also, specific treatment for any underlying disorder should be given.

HYPERNATREMIA

Epidemiology

Hyponatremia is defined as a serum sodium concentration greater than 145 mEq/L. Hyponatremia invariably denotes hypertonic hyperosmolality and always causes cellular dehydration, even if just transiently. It is characterized by a deficit of TBW relative to total body sodium and can result either from net water loss, or, less commonly,
from hypertonic sodium gain. The primary problem is inadequate water intake, secondary to a defective thirst mechanism due to aging or a lack of access to fluid.

The inpatient incidence of hypernatremia ranges from 0.3% to 1%.\textsuperscript{110} Hypernatremia was reported in approximately 1% of hospitalized patients older than 60 years and up to 60% of febrile nursing home residents.\textsuperscript{111} The prevalence of hypernatremia in a study of 981 adults hospitalized in the ICU was 9% (2% had hypernatremia on admission and 7% developed hypernatremia during hospitalization).\textsuperscript{112} In a retrospective survey, it was concluded that hypernatremia could potentially be used as an indicator of quality of care in the medical ICU.\textsuperscript{113} The prevalence of hypernatremia in patients who present to the ED was 13%.\textsuperscript{114} The presence of hypernatremia is associated with a mortality rate of more than 40%.\textsuperscript{111} The change in the status of consciousness when hypernatremia was diagnosed was the single prognostic indicator associated with mortality.\textsuperscript{115}

Pathophysiology

As mentioned earlier, with aging, urinary concentration ability in the elderly is diminished, which reflects diminished tubular function. A healthy young adult can achieve a maximum urinary concentration of 1200 mOsm/kg, whereas a healthy older person can often only achieve a urine osmolality of 700 to 800 mOsm/kg, thus increasing the risk of developing hypernatremia in the geriatric patients. Furthermore, the sensitivity of thirst in older patients is also diminished, which predisposes them to the development of hypernatremia.\textsuperscript{64} In addition, the percentage of body water decreases with age, so equal volumes of fluid loss in older individuals may represent more severe dehydration than in younger individuals.\textsuperscript{116}

Clinical Presentation

The presence of severe symptoms usually requires an acute and large elevation in the plasma sodium concentration to above 160 mEq/L.\textsuperscript{117} Symptoms are usually nonspecific and include lethargy and weakness. Obtundation, stupor, coma, and seizures may accompany more severe hypernatremia.\textsuperscript{118} Intense thirst may be present initially, but it dissipates as the disorder progresses and is absent in patients with hypodipsia.\textsuperscript{111}

The following 4 signs were significantly and independently associated with hypernatremia in older adults: abnormal supraclavicular, skin turgor, abnormal thigh skin turgor, dry oral mucosa and recent change in consciousness. Abnormal skin turgor is defined as “tenting” lasting at least 3 seconds after 3 seconds of skin pinching.\textsuperscript{115} Serum glucose levels should be checked in all patients with these signs to rule out dehydration due to an osmotic diuresis caused by hyperglycemia. Serum creatinine, potassium, and calcium levels; osmolality; and BUN should be checked. Measurement of UO and urine osmolality helps in determining the cause. In a study, an elevated BUN/Cr ratio that coexisted with hypernatremia was sensitive in detecting patients with hypernatremic dehydration.\textsuperscript{115}

Chronic hypernatremia is associated with milder symptoms because of the adaptive response that is initiated promptly and consists of solute gain by the brain that tends to restore the lost water and normalizes brain volume.\textsuperscript{119} CT scan of the brain is appropriate to evaluate patients with hypernatremia because acute brain shrinkage can induce vascular rupture with cerebral bleeding and subarachnoid hemorrhages.\textsuperscript{120}

Box 3 mentions some factors that increase the risk of hypernatremia in elderly patients.\textsuperscript{121,122}
Causes and Approach

The cause of hypernatremia is typically evident from the routine history and physical examination; however, additional diagnostic tests of the AVP-renal axis may be needed to establish the diagnosis.

There are 4 major causes of hypernatremia: insufficient water intake, hypotonic fluid depletion, sodium overload, and transient transcellular water shift.

**Insufficient water intake**

Hypernatremia from inadequate water intake is usually a consequence of insufficient access to free water, an impaired or altered sensation of thirst, or neurologic injury with altered mental status.

Acquired hypothalamic structural lesions can result in a true defect of thirst and osmoregulation. This condition is called primary hypodipsia. Conditions that can cause primary hypodipsia include traumatic brain injury, brain tumors, granulomatous infiltration (ie, sarcoidosis), and vascular disease. Furthermore, conditions that cause delirium, or that result in a significant neurologic injury (ie, stroke) aggravate age-related declines in thirst and hypodipsia caused by hypothalamic lesions. Essential hypernatremia is a variant of primary hypodipsia, in which the osmotic threshold for AVP and thirst has been reset to a higher level than the normal baseline. The urine osmolality of these patients is elevated.

**Hypotonic fluid depletion**

In the setting of an elevated serum osmolality (>295 mOsm/kg H₂O), hypernatremia serum Na levels greater than 145 mmol/L with a urine osmolality of less than 800 mOsm/kg indicates a renal concentrating defect.

Renal loss of hypotonic fluid can be seen with an osmotic diuresis that is caused by an excess of urinary solute, typically nonreabsorbable, that induces polyuria and hypotonic fluid loss, as seen in hyperglycemia (ie, diabetic ketoacidosis) or with the use of mannitol. The use of diuretics (ie, loop or thiazide diuretics) is also common in critically ill patients and can contribute to hypotonic urinary fluid losses. The relief of complete postrenal urinary obstruction can initially be associated with a large diuresis that may result in hypernatremia. In cases of renal loss of hypotonic fluid, the urinary

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**Box 3**

Risk factors for hypernatremia in elderly patient

- Age greater than 85 years.
- Female sex.
- Having more than 4 chronic conditions.
- Taking more than 4 medications.
- Limited mobility.
- Infections.
- Altered mental status.
- Hypertonic infusions.
- Tube feedings.
- Osmotic diuretics.
- Laxatives.
- Mechanical ventilation.
sodium concentration is usually greater than 20 mEq/L and the urine osmolality is less than 700 mOsm/kg.

Fluid losses from the gastrointestinal tract are generally hypotonic to serum, and, consequently, lead to hypernatremia if not replaced. These losses can occur from vomiting, nasogastric drainage, enterocutaneous fistulas, diarrhea, or the use of osmotic cathartic agents (ie, lactulose).

Insensible fluid losses from the skin (ie, sweat) and the respiratory tract (ie, evaporation) are generally hypotonic to serum; hypernatremia ensues in circumstances of increased insensible fluid loss, such as fever, diaphoresis, or tachypnea. Febrile illness in elderly individuals with decreased sensorium is the most common cause of hypernatremia. Upper respiratory tract, lung, and urinary tract infections are the most common causes for the fever. It has been suggested that in elderly patients with acute febrile disease, temporary hypernatremia may reflect an inadequate vasopressin response to the hyper-osmolar state. In all cases of extrarenal fluid loss, the urinary sodium concentration is less than 20 mEq/L and the urine osmolality is greater than 700 mOsm/kg.

Diabetes insipidus (DI) is a condition that is characterized by the excretion of large amounts of severely diluted urine (<700 mOsm/kg and often <200 mOsm/kg). There are 2 types of DI: central DI (a consequence of a deficiency of AVP secretion) and nephrogenic DI (due to AVP resistance at the collecting tubules). These 2 types can be distinguished by administering exogenous AVP (dDAVP, 10 mcg intranasal, or vasopressin, 5 units subcutaneous). Urine osmolality increases by 50% in central DI, whereas no significant change occurs in nephrogenic DI. Even in the most severe forms of DI, hypernatremia does not develop unless there is a concomitant defect in thirst or restricted access to water.

Central DI is uncommon, and most cases can be linked to lesions or injury to the hypothalamus after pituitary surgery, traumatic brain injury, subarachnoid hemorrhage as well as with tumors, granulomatous infiltration, or autoimmune disease.

Nephrogenic DI can result from drugs, acute and chronic renal failure, obstructive uropathy, hypercalcemia, hypokalemia, and sickle cell disease. Lithium is the most common cause of drug-induced nephrogenic DI, followed by foscarnet and clozapine. Lithium causes nephrogenic DI by downregulation of AVP-2 receptors and/or reduced expression of AQP2 channels.

**Sodium overload**

Hypernatremia from pure sodium overload is rare and frequently iatrogenic. This condition is seen in excessive sodium bicarbonate administration during cardiopulmonary resuscitation, overcorrection of hyponatremia with hypertonic saline, hypertonic dialysate in peritoneal dialysis (PD) and hemodialysis (HD), and hypertonic enteral or parenteral hyperalimentation. Noniatrogenic causes include primary hyperaldosteronism and Cushing syndrome.

**Transient water shift into cells**

Transient hypernatremia is induced by intense exercise or prolonged convulsive seizure activity. This phenomenon typically occurs in the context of marked lactic acidosis and can transiently raise the serum sodium concentration by 10 to 15 mEq/L, which returns to normal within 10 to 15 minutes.

**Treatment**

The treatment of hypernatremia consists of addressing the underlying causes (eg, fever, diuretic use and so on) and correcting the hypernatremia. When hypernatremia
is associated with extra-cellular fluid (ECF) depletion that causes hemodynamic compromise, isotonic saline should be administrated initially to improve blood pressure and end-organ perfusion.

Serum electrolytes should be monitored at least daily, and more frequently (every 4 to 6 hours) if the patient is severely ill, so adjustments in therapy can be made accordingly. In addition, frequent neurologic examinations, assessment of mental status, pupil examination, and examination of motor strength and reflexes should be performed to assess for clinical deterioration because transient improvement followed by deterioration in the neurologic status suggests the development of iatrogenic cerebral edema.

The preferred route for administering fluids is the oral route or a feeding tube; if this is not feasible, fluids should be given intravenously. Only hypotonic fluid should be used to correct the hypernatremia, the choice includes pure water, ¼ isotonic saline (0.2% NaCl), and ½ isotonic saline (0.45% NaCl) with or without 5% dextrose. The more hypotonic the infusate, the lower the infusion rate that is required. The risk of cerebral edema increases with the volume of the infusate. The sodium concentration should be corrected with a rate of 0.5 to 1 mEq/L/h, with a maximum decrease of 10 mEq/L per 24-hour period.

Even in hypernatremia, the Adrogue formula\textsuperscript{118} can be used to predict the effect of 1000 mL of an infusate

\[
\text{Change in plasma sodium} = \frac{(\text{Infusate sodium} - \text{Plasma sodium})}{(\text{Total body water} + 1)}
\]

For example, in a 68-kg elderly man who presents with severe obtundation and a sodium concentration of 168 mEq/L 1 L of D5W (0 mEq/L sodium) decreases the serum sodium concentration by approximately 4.8 mEq/L, as calculated by \((0 - 168)/([0.5 \times 68] + 1)\). The goal is to reduce the sodium concentration by 10 mEq/L over a 24-hour period, and to do this we need 2.1 L of D5W (10/4.8). Furthermore, we should add 1.5 L to compensate for average obligatory water losses over the 24-hour period, therefore a total of 3.6 L should be administered for the next 24 hours at a rate of 150 mL/h.

Correction of hypernatremia in hospitalized adults within 4 days was associated with a higher frequency of improvement in the level of consciousness. Correction that extended over more than 4 days was associated with a tendency toward permanent loss of cognitive function.\textsuperscript{117}

There is also an association between hypokalemia and hypernatremia.\textsuperscript{117} The correction of hypokalemia is important because it reverses the defect in the concentrating ability of the kidney and thus improves water conservation.\textsuperscript{139}

In patients with central DI with altered mental status or lacking access to water, the polyuria can usually be controlled by hormone replacement with AVP analogs such as desmopressin (dDAVP). In nephrogenic DI, the offending drug should be discontinued and the hypercalcemia and hypokalemia should be corrected. A low-salt and low-protein diet can also help, and thiazides with or without amiloride and nonsteroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to be useful.\textsuperscript{140}

In patients with sodium overload, a combination of furosemide and free water such as D5W can be tried. Furosemide alone should not be given because it will exacerbate hypernatremia by causing the excretion of hypotonic urine. Patients may need dialysis if severe renal failure is present.\textsuperscript{140}

**Summary**

Hypernatremia is common in older patients, especially those who are frail, bedridden, and febrile. Hypernatremia often presents in geriatric patients as dehydration and altered mental status. Initially, very hypernatremic dehydrated older patients need
normal saline to correct severe hypovolemia; however, once they are hemodynamically stable, they require hypotonic fluids. The hypernatremia should be corrected slowly to avoid cerebral edema. Underlying causes should also be promptly identified and managed appropriately.

**HYPERCALCEMIA**

*Introduction*

Hypercalcemia is a very important and relatively frequent problem, especially in older patients. If not recognized and treated expeditiously, patients with hypercalcemia can have significant mortality and morbidity. The normal level of serum calcium is 8.7 to 10.4 mg/dL (2.12–2.55 mmol/L). Mild hypercalcemia is when the serum calcium levels are 10.5 to 12 mg/dL (2.55–3 mmol/L), and in moderate hypercalcemia, the serum calcium level is 12 to 14 mg/dL (2.55–3.0 mmol/L).

Severe hypercalcemia is defined as calcium levels greater than 14 mg/dL (>3.5 mmol/L) and always requires emergency management. However, it must be emphasized that the level of calcium alone does not determine the severity of symptoms. Severe symptoms requiring emergency management may occur even at lower levels of calcium (12–14 mg/dL) in geriatric patients and in patients who have rapidly rising levels of calcium. The term hypercalcemic crisis is often used for patients who require emergency management of their elevated calcium levels.

When evaluating an abnormal calcium level, it is important to measure the patient’s albumin as well as the serum calcium levels because about 40% of serum calcium is protein bound, mainly with albumin; 50% is in the active ionized form; and 10% is bound to other anions. Low serum albumin levels can give falsely low serum calcium levels, and high serum albumin levels can give falsely high serum calcium levels. The following equations can be very useful in correcting the serum calcium level when serum albumin levels are abnormal:

For values in mg/dL: Corrected Ca = Measured total Ca + 0.8 × (4.5 – albumin)

For values in mmol/L: Corrected Ca = Measured total Ca + 0.02 × (40 – albumin)

Measuring the ionized calcium levels directly when available can sometimes be very useful, especially in acutely ill older patients who often are hypoalbuminemic. This measurement avoids errors related to abnormal albumin levels. Normal ionized serum calcium levels range from 4 to 5.6 mg/dL (1–1.4 mmol/L).

*Epidemiology*

Hypercalcemia is a fairly frequent problem. Severe hypercalcemia accounts for more than 3% of hospital admissions from the ED. More than 90% of cases are due to either primary hyperparathyroidism or malignancy. In the United States, 25 per 100,000 persons in the general population have primary hyperparathyroidism, which is the most frequent cause of mild hypercalcemia. The occurrence of primary hyperparathyroidism increases with age, and its incidence in older women is 250 per 100,000. Malignancy-related hypercalcemia is the most common cause of hypercalcemic crisis. More than 20% of patients with cancer develop hypercalcemia during the course of their disease. The mortality rate of patients with hypercalcemia because of malignancy is very high. Because the incidence of malignancy increases with age, the incidence of malignancy-associated hypercalcemia also increases with age. In the Netherlands, the overall incidence of hypercalcemia in elderly women is 3%.
Other causes of hypercalcemia are also present in geriatric patients, but are much less common. Immobilization can cause hypercalcemia, which is usually mild, but it can rarely cause severe hypercalcemia and can also exacerbate the hypercalcemia associated with hyperparathyroidism and malignancy.\textsuperscript{151} Medications, especially thiazides, have been noted to cause hypercalcemia, in older patients, and also worsen the hypercalcemia associated with other causes, especially primary hyperparathyroidism.\textsuperscript{150–152} Other medications that can cause and/or exacerbate hypercalcemia because of other causes in geriatric patients are vitamin D,\textsuperscript{153} vitamin A,\textsuperscript{154} retinoic acid,\textsuperscript{155} lithium,\textsuperscript{156} calcium carbonate causing the milk-alkali syndrome,\textsuperscript{157} and tamoxifen.\textsuperscript{158} In addition to hyperparathyroidism, other endocrine diseases have been noted to cause hypercalcemia, most prominently hyperthyroidism.\textsuperscript{159} Other illnesses that have been reported as causing hypercalcemia in older patients are granulomatous diseases, especially sarcoidosis,\textsuperscript{160,161} renal-disease-related secondary and tertiary hyperparathyroidism, and Paget disease.\textsuperscript{152}

**Pathophysiology**

Hypercalcemia occurs when the amount of calcium entering the body via the small intestine exceeds the amount of calcium being excreted through the kidney and being deposited in bones. Hypercalcemia can occur when an excess of calcium is absorbed through the intestine, when there is an increase in bone resorption, or when the excretion of calcium through the kidney is decreased. More than one of these mechanisms acting in concert may cause hypercalcemia.

Serum calcium levels are regulated by the action of 3 hormones: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and calcitonin. There is feedback between these hormones that normally keeps serum calcium levels within the normal range. Hypercalcemia occurs when this regulatory system becomes overwhelmed by an excess of PTH; the secretion by tumor of a parathyroid-hormone-related protein (PTHrP), which has the same effects as PTH; an excess of calcitriol, which primarily increases absorption of calcium in the gastrointestinal tract; an increase in local bone resorption; a decrease in the excretion of calcium through the kidney; or an increased amount of calcium being ingested and absorbed in the gastrointestinal tract.

In older patients, the ability to respond to an excess of calcium and maintain homeostasis is much less than in younger patients and the incidence of the 2 most common diseases that cause hypercalcemia, that is, hyperparathyroidism and malignancy, is greater.\textsuperscript{148,150,162} Therefore, it is not surprising that severe hypercalcemia is much more common in older patients.\textsuperscript{150} Box 4 demonstrates why older patients are more likely to develop severe hypercalcemia.

<table>
<thead>
<tr>
<th>Reasons for increased severe hypercalcemia in older patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased incidence of malignancy</td>
</tr>
<tr>
<td>Increased ingestion of drugs that increase calcium</td>
</tr>
<tr>
<td>Decreased renal clearance of calcium</td>
</tr>
<tr>
<td>Increased absorption of calcium in the gastrointestinal tract</td>
</tr>
<tr>
<td>Increased incidence of hyperparathyroidism</td>
</tr>
<tr>
<td>More immobility</td>
</tr>
<tr>
<td>Increased incidence of dehydration because of comorbidities</td>
</tr>
<tr>
<td>Increased resorption of bone</td>
</tr>
</tbody>
</table>
Most cases of primary hyperparathyroidism in geriatric patients are due to parathyroid adenomas, and most of these patients have only mild elevations of their serum calcium levels and are relatively asymptomatic. However, some of these elderly patients eventually become symptomatic and therefore need to be closely followed up. Hyperparathyroidism increases serum calcium levels by increasing calcitriol production, which increases gastrointestinal absorption. An excess of PTH also increases calcium absorption in the distal renal tubules and increases resorption of bone, although this effect is opposed by deposition of excess calcium in the bone because of the action of calcitonin, which also opposes the action of PTH on the kidney. Also, some parathyroid adenomas may decrease their secretion of PTH in response to the hypercalcemia. This response may explain why very high levels of calcium (>14 mg/dL, >3.5 mmol/L) are not usually found in isolated primary hyperparathyroidism. When severe hypercalcemia is found in a patient with primary hyperparathyroidism, something that exacerbates the effects of the hyperparathyroidism, such as the ingestion of thiazides, calcium carbonate, excessive vitamin D, or immobilization, should be considered.

Hypercalcemia associated with malignancy is usually more severe than that due to primary hyperparathyroidism. Hypercalcemia associated with malignancy is most commonly caused by multiple myeloma, metastatic breast cancer, or metastatic lung cancer and is due to increased local osteoclastic activity in the involved bone. Metastatic invasion of bone by solid tumors, lymphomas, and leukemias causes hypercalcemia by increasing the local osteoclastic activity. Nonmetastatic solid tumors usually cause hypercalcemia by the secretion of PTHrP. Lymphomas can also cause hypercalcemia by increased levels of calcitriol produced by macrophages. Ghazi reported the case of an older patient with lymphoma caused by both tumor secretion of PTHrP and calcitriol.

Hyperthyroidism causes hypercalcemia that is usually mild by increasing resorption of bone. Granulomatous diseases, such as sarcoidosis, can cause hypercalcemia by increasing the level of calcitriol and thereby increasing calcium absorption in the small intestine. Thiazides increase serum calcium levels by decreasing the urinary excretion of calcium. Lithium increases calcium levels by increasing the set point of PTH. Vitamin A causes hypercalcemia by increasing bone resorption.

Clinical Effects of Hypercalcemia

Hypercalcemia causes hyperpolarization of cell membranes. Patients with mild elevations of calcium levels (10.5–12 mg/dL) are often asymptomatic. When the serum calcium level becomes higher than this, multiple organ systems can be involved and cause a multitude of symptoms. The classical mnemonic “stones, bones, moans, and groans” refers to pain from renal stones; bone pain; moans because of abdominal pain, which may be caused by peptic ulcer disease or pancreatitis; and psychic moans because of altered mental status, all of which may be seen with hypercalcemia, especially when caused by primary hyperparathyroidism. However, in older patients, symptoms may not be “classical” and may be “nonspecific.” The diagnosis of hypercalcemia should be strongly considered whenever an older patient presents with altered mental status or new-onset psychiatric symptoms and/or vague gastrointestinal symptoms, especially if there is a history of carcinoma.

Neuromuscular and neuropsychiatric symptoms include impaired concentration, anxiety, depression, confusion, altered mental status, fatigue, and muscle weakness. More severe symptoms, such as lethargy, stupor, and coma may occur with very high levels of serum calcium and are more common in geriatric patients.
Gastrointestinal symptoms, especially anorexia, nausea, vomiting, and constipa-
tion, are common. Abdominal pain, peptic ulcer disease, and pancreatitis occur, but are less common.\textsuperscript{170,171}

Important renal manifestations are polyuria, nephrolithiasis, and acute and chronic renal failure, which may result from nephrocalcinosis. Hypercalcemia causes a nephro-
rogenic DI syndrome that interferes with the ability to concentrate urine.\textsuperscript{152} The ensuing polyuria, along with the gastrointestinal symptoms of hypercalcemia, can cause severe dehydration. This dehydration and the subsequent fall in GFR lead to decreased excretion of calcium and worsening of the hypercalcemia and its symp-
toms. A vicious cycle of worsening dehydration and hypercalcemia results from this.

Bone pain is commonly seen with both hyperparathyroidism and malignancy. Severe osteoporosis and cystic lesions of bone more commonly occur with primary hyperparathyroidism.\textsuperscript{172}

Hypercalcemia can have adverse cardiovascular effects. Acute severe hypercal-
cemia causes a short QT interval because of shortening of the action potential of the heart.\textsuperscript{173} However, rare cardiac arrhythmias have occurred in patients with acute severe hypercalcemia, including ventricular fibrillation, bradycardia, and conduction defects.\textsuperscript{174} Also, ST elevation mimicking an acute myocardial infarction has been noted in patients with acute severe hypercalcemia.\textsuperscript{175} Chronic effects of hypercal-
cemia, such as calcification of heart valves, coronary arteries, and myocardial fibers; cardiomyopathy; and hypertension have been described in patients with
hyperparathyroidism.\textsuperscript{176}

\textbf{Clinical Evaluation}

The possibility of severe hypercalcemia must be considered in any older patient who
presents with acutely altered mental status.\textsuperscript{150} Initially, clinicians should use focused
history, physical examination, and laboratory evaluations to evaluate for other causes
of altered mental status in geriatric patients, including infection, adverse drug reac-
tions, hypoglycemia, hyperglycemia, dehydration, hyponatremia, and acute neuro-
logic, cardiac, or pulmonary events.\textsuperscript{177}

When the initial elevated serum calcium level returns, establishing the diagnosis of
hypercalcemia, a thorough history and physical examination should be performed
looking for the clinical effects of hypercalcemia and their severity and clues to the
various causes of hypercalcemia. These causes include malignancies, hyperparathy-
roidism, medications (thiazides, lithium, vitamin D, vitamin A, calcium carbonate,
tamoxifen, and theophylline), hyperthyroidism, immobilization, Paget disease, and
granulomatous diseases (sarcoidosis and tuberculosis). On physical examination, findings that should be looked for are abnormal mental status, muscle weakness,
signs of dehydration, corneal calcifications, neck masses, lymphadenopathy, and
other signs of malignancy.

\textbf{Laboratory Evaluation}

Measurement of serum calcium levels should be repeated for confirmation and to
monitor the effects of therapy. As noted previously, serum calcium levels should be
corrected for any abnormality of the patient’s serum albumin levels. Several authorities
prefer to follow ionized calcium levels to avoid this problem.\textsuperscript{145} Once the diagnosis of
hypercalcemia has been confirmed, tests should be performed to confirm the cause of
the hypercalcemia. Tests should be performed to differentiate between malignancy
and hyperparathyroidism, the 2 most common causes of hypercalcemia in the elderly.

PTH levels should be checked. Elevated PTH levels in the face of hypercalcemia
confirm the diagnosis of hyperparathyroidism. Other laboratory clues that point to
hyperparathyroidism are low serum phosphate and high serum chloride levels. Imaging studies of the head and neck may be needed to further delineate the exact cause of the hyperparathyroidism before surgery. PTHrP secretion by many solid tumors can cause hypercalcemia, and its levels can be measured.\textsuperscript{178} Appropriate imaging should be done to diagnose suspected malignancy.

Thyroid function tests should be sent if hyperthyroidism is suspected as a possible cause of the hypercalcemia.

Hypercalcemia caused by overdosing vitamin D supplements can be diagnosed by measuring 25-hydroxyvitamin D levels. Granulomatous diseases, such as sarcoidosis, and Hodgkin lymphoma can cause hypercalcemia by increasing 1,25-dihydroxyvitamin D (calcitriol) levels, and this can be measured.\textsuperscript{152} These entities usually have both high serum calcium and phosphate levels.

Table \ref{table5} gives a diagnostic approach for the evaluation of hypercalcemia in geriatric patients.

\section*{Management of Severe Hypercalcemia in Older Patients}

Patients with severe hypercalcemia, which is defined as calcium levels greater than 14 mg/dL, and patients with mental status changes and calcium levels greater than 12 mg/dL require acute management in the ED and admission.\textsuperscript{142} The goals of management are resuscitating the patient as needed, improving symptoms by expeditiously lowering serum calcium levels, and treating the underlying cause. As always, airway, breathing, and circulation need to be evaluated and supported as required. Severe hypercalcemia can cause coma that could adversely affect the airway and breathing. Hypercalcemic crisis often causes severe hypovolemia, requiring aggressive fluid resuscitation. Severe hypercalcemia can occasionally cause arrhythmias, and therefore, these patients should have cardiac monitoring.

The best way to rapidly lower calcium levels is hydration with normal saline, intravenous bisphosphonates, and parenteral calcitonin. Hydration with intravenous normal saline should be the initial treatment given in the ED.\textsuperscript{179} The amount and rate of intravenous saline given to a particular patient depends on the patient’s initial volume status, the serum calcium level, and comorbidities, such as congestive heart failure and renal failure. Older patients are less likely to tolerate overhydration and must be

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Cause of Hypercalcemia} & \textbf{Appropriate Diagnostic Tests} \\
\hline
All causes & Directed history: history of malignancy, comorbidities, bone pain, immobilization, medications \\
\hline
All causes & Directed physical examination: vital signs, signs of dehydration, neck masses, lymphadenopathy, signs of malignancy \\
\hline
Hyperparathyroidism & PTH level and if high, imaging of neck \\
\hline
Malignancy & PTHrP level, malignancy workup with appropriate imaging, serum and urine protein electrophoresis, biopsy as appropriate \\
\hline
Hyperthyroidism & Thyroid function tests \\
\hline
Granulomatous disease & Chest radiograph, ACE, lymph node biopsy, calcitriol level \\
\hline
Vitamin D intoxication & 25-hydroxyvitamin D level \\
\hline
Renal disease & BUN, creatinine, urine pH, and electrolytes \\
\hline
Paget disease & Bone radiographs \\
\hline
\end{tabular}
\caption{Evaluation for hypercalcemia in older patients}
\end{table}

\textit{Abbreviation:} ACE, angiotensin-converting enzyme.
closely monitored for signs of fluid overload. In special situations, central venous pressure monitoring may be useful. The aim of saline hydration is to restore the normal intravascular volume and promote good UO. In most cases, it is recommended to start with a rate of 200 to 300 mL/h and then adjust the rate to maintain a UO of 100 to 150 mL/h, once the patient is euvoletic. If the patient develops signs of fluid overload, furosemide can be used. The routine use of massive saline infusion and furosemide are no longer recommended.

Bisphosphonates, which act by inhibiting bone resorption by osteoclasts, have become a mainstay in the treatment of moderate and severe hypercalcemia, especially when caused by malignancies. Intravenous zoledronic acid (ZA), 4 mg, given over 15 minutes and intravenous pamidronate, 60 to 90 mg, given over 2 hours are the bisphosphonates available for the treatment of severe hypercalcemia. ZA is preferred by many experts because it is more potent, it is given more easily, and its effect on serum calcium lasts longer than that of pamidronate.

Both medications require dosage adjustment in patients with renal disease. Because both drugs take 2 to 4 days to show their maximum effect, patients with severe hypercalcemia are also treated with hydration and calcitonin, which work faster. Salmon calcitonin, which works by both increasing urinary excretion of calcium and decreasing bone resorption, has a fairly rapid onset of action (4–6 hours), but its therapeutic effect only lasts for 48 hours. Therefore, it is mainly used for treating severe hypercalcemia to gain time until the more sustained action of the bisphosphonates can take effect. Salmon calcitonin is given as a dose of 4 IU/kg intramuscularly or subcutaneously every 12 hours for 3 doses.

**Treatment of Specific Causes and Special Situations**

Medications that cause hypercalcemia should be stopped. Glucocorticoids are used to treat hypercalcemia caused by excessive intake of vitamin D or the overproduction of calcitriol that occurs in patients with granulomatous diseases, Hodgkin lymphoma, and multiple myeloma. Prednisone is usually given at a dose of 40 mg/d.

Cinacalcet, a calcimimetic drug, is used to treat severe hypercalcemia in patients with parathyroid carcinoma and patients undergoing dialysis with secondary hyperparathyroidism. The starting dose is 30 mg orally once a day, and it is titrated up by 30 mg/d every 2 to 4 weeks depending on the calcium and PTH levels. Gallium nitrate and cisplatin have been used to treat hypercalcemia due to malignancy that is refractory to treatment with bisphosphonates. Patients with primary hyperparathyroidism and severe hypercalcemia should have urgent parathyroid surgery once their condition has been stabilized.

Dialysis, especially HD with no calcium in the dialysis fluid, can be used for severe hypercalcemia resistant to other therapies and in patients with fluid overload due to congestive heart failure or renal failure, in which hydration cannot be used.

**Summary**

Hypercalcemia in geriatric patients is relatively common, and has significant morbidity and mortality. Common clinical manifestations of hypercalcemia in older patients are altered mental status, gastrointestinal complaints, bone pain, and dehydration. Important causes of hypercalcemia to consider in older patients are malignancy, hyperparathyroidism, hyperthyroidism, medications, granulomatous diseases, and immobilization. Management of severe hypercalcemia in geriatric patients should consist of hydration with normal saline, intravenous bisphosphonates, and calcitonin and treating the underlying cause.
ACUTE RENAL FAILURE IN GERIATRIC PATIENTS

Introduction and Epidemiology

Acute renal failure, now referred to as AKI, is much more common in the older population, a trend compounded by the fact that older people are rapidly becoming a bigger percentage of the population. Overall, AKI is becoming more common.²⁸ Old age seems to be a risk factor for AKI.²⁸,²⁹ In a recent study, the frequency of AKI and acute on chronic failure were much higher than they were previously thought with an incidence of 1.811 per million population and 336 per million population, respectively. The median age of the patients who developed AKI was 76 years and that of the patients who developed acute on chronic renal failure was 80.5 years.³⁰ Therefore, AKI is largely a geriatric disease.

In addition to a new name, there are also new classification systems for AKI, with the most commonly used system being the risk, injury, failure, loss, and ESRD (RIFLE) classification.³¹ This classification is based on an increase in serum creatinine level, a decrease in GFR, or a decrease in UO as follows:

1. Risk: Increase in serum creatinine level × 1.5, decrease in GFR by 25%, or UO less than 0.5 mL/kg/h for 6 hours.
2. Injury: Increase in serum creatinine level × 2, decrease in GFR by 50%, or UO less than 0.5 mL/kg/h for 12 hours.
3. Failure: Increase in serum creatinine level × 3; decrease in GFR by 75%, or serum creatinine level of 4 mg/dL or more, with an acute increase of more than 0.5 mg/dL; UO less than 0.3 mL/kg/h for 24 hours, or anuria for 12 hours.
4. Loss: Persistent acute renal failure (ARF), complete loss of kidney function for more than 4 weeks.
5. End-stage renal disease: Loss of kidney function for more than 3 months.

AKI has a very poor prognosis in older patients, especially when it is associated with sepsis, and/or multiorgan failure,³² with mortality rates as high as 75%.³³ Older patients are not only more likely to develop AKI, with the associated increased mortality and morbidity, but also more likely to have impaired recovery of renal function.³⁴ They are also more likely to develop chronic renal disease and ESRD from AKI.³⁵ Therefore, it is imperative that steps be taken in older patients to prevent AKI, to look for it and diagnose it early, and to treat it expeditiously when it occurs.³⁶

Pathophysiology and Causes

Structural and functional changes occur with aging that make the kidney more susceptible to AKI.³⁷ These changes have been previously described in this article. In addition to these changes in the kidney, older patients also have age-related changes in the cardiovascular and immunologic systems that make them more prone to AKI.³⁸ The elderly are more likely to have comorbidities that are important risk factors for the development of AKI, including chronic kidney disease, diabetes, hypertension, coronary artery disease, congestive heart failure, and atheroembolic disease.³⁹,⁴⁰,⁴¹,⁴²,⁴³ Recently, “cardiorenal syndrome” has been recognized as an important entity. Cardiorenal syndrome is a disorder of the heart and kidney whereby acute or chronic dysfunction of one organ causes or exacerbates acute dysfunction of the other organ and increases the overall mortality and morbidity.⁴⁴ Patients with congestive heart failure who have a significant acute decrease in renal function have a 3 times greater mortality rate than those who have normal renal function.⁴⁵ Important causes of AKI in the older patients are sepsis, hypovolemia, medications, vascular disease, and urinary obstruction. These causes are very important to
consider because they are potentially reversible if found early and treated appropriately and expeditiously.\textsuperscript{193} The cause of AKI is often multifactorial in geriatric adults.\textsuperscript{193}

Owing to changes in the immune system with aging, older patients have an increased susceptibility to serious infections.\textsuperscript{201} Often, these infections present atypically in geriatric adults and are undetected until late in the disease course. Because sepsis is a leading cause of AKI and a prominent source of morbidity and mortality in older patients, it is imperative that physicians consider and look for occult infections in acutely ill older patients.\textsuperscript{202}

The cause of AKI is commonly classified into 3 categories: prerenal (33% of cases in older adults), intrinsic (58% of cases in older adults), and postrenal (9% of cases in older adults). Prerenal AKI, usually due to hypovolemia, is the second most common cause of acute renal failure in geriatric patients.\textsuperscript{193} As noted previously, older patients are much more likely to become dehydrated than younger adults. If these patients are allowed to become significantly hypovolemic, the kidneys become ischemic, and unless this situation is detected early and the patient treated aggressively with fluids, irreversible intrinsic renal failure due to acute tubular necrosis (ATN) occurs, which increases morbidity and mortality. For example, older surgical patients, who became hypovolemic in the perioperative period, are more likely to develop acute renal failure postoperatively, with significant complications related to the AKI.\textsuperscript{203} In fact, surgery puts older patients at risk for AKI, and any factor, such as hypovolemia, infection, and nephrotoxic medications, that further adds to this risk should be avoided, monitored, and corrected, if found.\textsuperscript{203,204}

Intrinsic AKI, particularly ATN, is the most common type of acute renal failure in geriatric patients and usually occurs after an ischemic or toxic event.\textsuperscript{193} Nephrotoxic medications, especially NSAIDs, loop diuretic, laxatives, radiocontrast dyes, and antibiotics, such as aminoglycosides, are common causes of this type of AKI in geriatric patients.\textsuperscript{205} Older patients are more likely to have nephrotoxic reactions to medications than younger patients, because the older adults are more likely to be on more medications and have more difficulty in metabolizing and excreting medications because of preexisting comorbidities.\textsuperscript{206,207} Therefore, all physicians must be very careful when prescribing medications to older patients. Potentially nephrotoxic medications should be avoided when possible, and proper dosing should be checked when prescribing new medications to geriatric patients. “Start low and go slow” is a good general rule to follow when prescribing new medications in older patients.

Vasculitis is another important cause of intrinsic acute renal failure in older patients that should be looked for because it not only can be life threatening but also can be treated if detected early.\textsuperscript{193,208}

Postrenal AKI, caused by urinary tract obstruction, is almost exclusively seen in older patients. There are really no good studies to show how common urinary obstruction is in the general population; however, surveys in older men showed that 20% to 35% of older men had moderate symptoms of urinary obstruction.\textsuperscript{209} Autopsy studies showed that the incidence of hydronephrosis was 3.8% in adults and 2% in children.\textsuperscript{209} Although most commonly seen in older men with benign prostatic hypertrophy or prostatic cancer, urinary tract obstruction can also be seen in older women and is caused by pelvic malignancy, uterine prolapse, hypotonic bladder, or medications, such as anticholinergics and narcotics.\textsuperscript{193} Urinary tract obstruction is another very important cause of AKI not to miss because it can sometimes be easily treated by relieving the obstruction early before significant permanent kidney damage has occurred. With complete obstruction, renal damage can be seen in 12 to 24 hours; however, the amount of permanent damage and recovery of renal function depends on the duration and level of obstruction, preexisting renal function, and the presence
of comorbidities or infection. Once the diagnosis of urinary obstruction is considered, a transurethral catheter should be placed into the bladder. This procedure should be performed in a sterile manner. Plenty of lubricant should be used. Usually, in an adult, a 16-French Foley catheter can be used. If this catheter cannot be passed because of a urethral stricture or an enlarged prostate, a smaller-sized catheter can be tried. If this catheter also cannot be passed, then a Crudet catheter can be tried, either by the emergency physician or the urologist, depending on the emergency physician’s level of skill and comfort with this procedure. If this procedure is unsuccessful, then urology should be consulted, and then the consultant can try filiform catheters or can perform a suprapubic cystotomy. Once the obstruction is relieved, the bladder should be completely drained, and clamping of the catheter is not necessary. Post-obstructive diuresis is an uncommon complication of relieving urinary obstruction. It is recognized when the patient continues to pass more than 200 mL/h for more than 2 hours. Urinary losses should be replaced with intravenous half-normal or normal saline, and electrolytes, such as potassium and magnesium, should be monitored and replaced as needed.

Box 5, Table 6 show the common causes of AKI in geriatric patients.

**Clinical Manifestations and Evaluation**

A comprehensive history, including medication history, and physical examination should be done. Clinicians should evaluate for symptoms and signs of uremia, such as weakness, anorexia, vomiting, altered mental status, seizures, signs of fluid overload, and pericarditis. However, these are late findings, and any very ill elderly patients should have appropriate laboratory testing to evaluate renal function. The history and physical examination should also focus on finding possible causes of the AKI, as noted earlier, that may be treatable if found early. The most important symptoms and signs to note are evidence of dehydration, infection, drug toxicity, urinary tract obstruction, cardiovascular disease, or vasculitis. It is very important to note these signs and symptoms, because they point to underlying causes that if treated appropriately early on, may prevent ongoing AKI and decrease subsequent morbidity and mortality. Special attention should be given to the vital signs and to the volume status of the patient, noting signs of dehydration or fluid overload.

**Box 5**

**Common causes of acute kidney injury in older patient**

- Sepsis/Infection
- Medications
- Renal ischemia & renal vascular complications
- Peri/Post-operative complications
- Acute cardiac complications
- Dehydration
- Contrast dye
- Vasculitis
- Urinary obstruction
- Toxins (myoglobin, hemoglobin, etc.)
Laboratory evaluation is used to make the diagnosis of AKI, to help differentiate between the various causes of AKI, and to look for complications of AKI. As per the RIFLE criteria, an acute increase in serum creatinine levels, a decrease in the GFR, and/or a decrease in urinary output are now the standards for making the diagnosis of AKI. Unfortunately, the level of serum creatinine is not a very accurate marker for AKI in the elderly, because it increases relatively late, is influenced by muscle mass and the hydration status of the patient, and tends to be "falsey" low in older patients. Although not currently available for general use, several biomarkers have been proposed to more accurately diagnose acute renal failure in older patients, especially cystatin C. Cystatin C is a nonglycosylated 13-kDa protein, which is believed to be more accurate in estimating GFR than creatinine levels because it seems to be less influenced by the muscle mass and diet. GFR decreases with age, and cystatin C may better estimate true renal function than creatinine in older patients because it is not affected by muscle mass. Cystatin C levels have been shown to increase about 1 to 2 days earlier than the serum creatinine level in patients developing AKI. Cystatin C thus seems to be a much better biomarker for detecting AKI in older patients than the serum creatinine.

Several laboratory tests may help in differentiating and diagnosing the different causes of AKI, especially between prerenal and intrinsic acute renal failure. A high BUN/serum creatinine ratio (>20) suggests a prerenal cause of the AKI; however, the sensitivity and specificity is not very good and other entities, such as gastrointestinal bleeding and the use of the sulfonylurea class of drugs, can cause an elevated BUN/creatinine ratio. A low fractional excretion of sodium (<1%), low urine sodium concentration (<20 mEq/L), and high urine osmolality (>500 mOsmol/kg) all suggest a prerenal cause for the AKI, rather than ATN. However, because of the frequent use of diuretics in geriatric patients, and the increased possibility of chronic renal disease in older patients, these findings are not always accurate in older patients. Urinalysis should be done to look for leukocytes, hematuria, protein, and casts to help in diagnosing infection, glomerulonephritis, and ATN. The presence of white blood cells (WBCs) and WBC casts would suggest the diagnosis of urinary tract infection or acute interstitial nephritis. Positive result of nitrite test is very specific for infection, but unfortunately not sensitive. Presence of bacteria on an unspun specimen of urine indicates infection. The presence of red cell casts would suggest the diagnosis of glomerulonephritis. The presence of granular cell casts, tubular cells, or tubular cell casts would suggest the diagnosis of ATN. If the urine dipstick tests positive for blood but no red cells are seen on microscopic examination, either rhabdomyolysis or hemolysis is indicated. The serum creatinine kinase level would be very high with rhabdomyolysis. UO should be closely followed. Ultrasonography should be performed to look for urinary obstruction, which is much more common in older patients. CT scan can be performed to look for renal stones and obstruction if clinically suspected, but intravenous contrast should not be used.

### Table 6

<table>
<thead>
<tr>
<th>Causes of AKI in Older Patients</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>33</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>58</td>
</tr>
<tr>
<td>Postrenal</td>
<td>9</td>
</tr>
</tbody>
</table>

### Diagnostic and Therapeutic Management Strategies

![Table 6](image.png)
Complications of severe AKI should be looked for, including hyperkalemia, metabolic acidosis, fluid overload, and pericarditis. The diagnosis of fluid overload is made clinically. The patient may complain of shortness of breath and swelling of the extremities. On examination, the clinician may find tachypnea, tachycardia, jugular venous distention, rales, and peripheral edema. A chest radiograph may show signs of vascular congestion and also helps diagnose other causes of shortness of breath, such as pneumonia, if present. B-type natriuretic peptide BNP levels are elevated in renal disease, as well as in patients with congestive heart failure. Very high levels of BNP may indicate the presence of concomitant CHF in patients with renal failure, but the clinical usefulness of BNP in the setting of renal failure is still unclear. Acute uremic pericarditis is also mainly a clinical diagnosis. Patients complain of sharp chest pain that is often pleuritic and may be worse on lying down. A pericardial friction rub may sometimes be heard, but it is transient and usually disappears as pericardial fluid accumulates. Electrocardiogram (ECG) early on may show diffuse ST elevations, but as fluid accumulates in the pericardial sac, these changes disappear and low voltage and electrical alternans may be seen. Bedside ultrasonography can be very useful in diagnosing pericardial effusion and pericardial tamponade. In acute severe AKI, as compared with ESRD that has occurred from progression of chronic renal failure, complications such as uremic symptoms, hyperkalemia, and metabolic acidosis often occur at relatively lower levels of creatinine and BUN. Although, patients with AKI are at risk for developing ESRD, not all patients do so, and some recover partially or even completely and do not require lifetime dialysis like the ESRD patients do. It is therefore very important to aggressively look for and treat the underlying causes and acute complications of AKI.

Management

In the ED, management priorities emphasize the treatment of life-threatening complications of renal failure, such as respiratory failure, pulmonary edema, hyperkalemia, and metabolic acidosis.

"An ounce of prevention is worth a pound of cure" when it comes to managing acute renal failure in older patients. Steps must be taken to prevent the AKI from getting worse because older patients have high mortality and morbidity with acute renal failure. Unless there is obvious evidence of fluid overload, these patients should be given intravenous volume replacement, but they must be carefully monitored because older patients are more prone to become fluid-overloaded, with resultant increased morbidity. Nephrotic drugs must be stopped, and any new drug that is given must be given in renal appropriate doses. If there is any evidence of urinary obstruction, it must be relieved. A urinary catheter should be placed to relieve the obstruction, and the UO should be followed. Urology consultation may sometimes be required. As noted earlier, permanent kidney damage can occur within 12 to 24 hours after acute complete urinary tract obstruction occurs. Therefore, if urgent urologic consultation is not available, steps should be taken to relieve bladder obstruction by passing a urinary catheter into the bladder. Special techniques such as using a Crudet catheter can be tried. As previously noted, specific underlying causes, such as sepsis and vasculitis, should be looked for and appropriately treated.

Complications of acute renal failure, such as hyperkalemia and fluid overload, must be treated. Severe hyperkalemia, which is defined as serum potassium levels greater than 7 mEq/L, if not rapidly treated has a mortality of 67%. However, it should be noted that it is not only the absolute level of serum potassium that matters but also the rate of increase of the serum potassium levels. The faster the increase of the serum
potassium levels, the more is one likely to have symptoms and signs of hyperkalemia. Severe hyperkalemia may manifest itself on the ECG as QRS widening, disappearance of the P wave, and arrhythmias, but there have been reports of severe hyperkalemia with minimal ECG changes. Until dialysis can be instituted, life-threatening hyperkalemia can be treated with calcium, insulin and glucose, and sodium bicarbonate, although it seems to work well only when the patient has significant metabolic acidosis and albuterol nebulization. Although ion exchange resins, such as kayexalate with sorbitol, are commonly used, there is no good evidence that they really work, and they may cause severe gastrointestinal problems. Vasodilators and loop diuretics may be effective to treat fluid overload until dialysis is available, but often, furosemide does not work in the setting of acute renal failure. There is no evidence that giving furosemide to patients with AKI and oliguria improves the prognosis and giving furosemide to patients who are not fluid overloaded may actually worsen morbidity and mortality. In one recent study of very elderly Chinese patients who developed AKI in the hospital, the use of α-keto acid seemed to be a protective factor and seemed to improve the prognosis of AKI (odds ratio = 0.656). However, more research needs to be done on the use of this agent before its use can be recommended.

Emergency renal replacement therapy (RRT), for example, HD, is indicated for pulmonary edema, severe uremic symptoms such as encephalopathy, severe hyperkalemia, severe metabolic acidosis, and pericarditis. Some studies showed that instituting dialysis prophylactically, for example, when the BUN was 100 or more, before the onset of life-threatening symptoms improved the outcome in these patients. Data from the Program to Improve Care in Acute Renal disease showed that the relative risk for death for patients who had RRT initiated at higher BUN values was 1.85. However, this result is still controversial because it was not supported by the results of other studies, and an adequately prospective randomized clinical trial is needed. Although older patients may have more complications with RRT, such as hypotension, bleeding, and dysequilibrium, than younger patients, they generally tolerate this procedure. In general, HD is preferred to PD because PD can have complications such as catheter leaks, peritonitis, and loss of serum albumin. Also, HD corrects acid–base and solute status faster in critically ill patients and causes less mortality when compared with PD. However, PD is usually effective and is less costly and complex than HD. PD is also less likely to cause hypotension than HD and does not require anticoagulation like HD does. Therefore, PD can be very useful as an alternative to HD in certain patients. There are some special regimens that have been used in unstable older patients, such as continuous RRT, but at present, there is insufficient evidence that these regimens are superior to the usual HD regimens. Sometimes, ethical considerations regarding instituting RRT in frail elderly patients arise, and the wishes of the patients and their family, not just the medical indications, must be taken into consideration.

Table 7 summarizes the important steps that should be taken in evaluating and treating older patients with AKI.

**Summary**

Acute renal failure is more common and has a worse prognosis in older patients. Underlying causes, such as sepsis, hypovolemia, drug toxicity, and urinary obstruction, must be looked for and treated expeditiously. Life-threatening complications, such as hyperkalemia and pulmonary edema, should be watched for and treated. The best treatment for the complications of AKI is RRT.
Table 7
Evaluation and management of AKI in older patients

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate airway, breathing, and circulation</td>
<td>Resuscitate as needed</td>
</tr>
<tr>
<td>Evaluate volume status</td>
<td>Hydrate with IV fluids as needed</td>
</tr>
<tr>
<td>Review all medications</td>
<td>DC all renal toxic medications and adjust doses of other medications</td>
</tr>
<tr>
<td>Look for underlying causes: infection, urinary</td>
<td>Treat any underlying causes, antibiotics for infection, relieve urinary</td>
</tr>
<tr>
<td>obstruction, renal ischemia, cardiac disease,</td>
<td>obstruction, etc.</td>
</tr>
<tr>
<td>vasculitis, rhabdomyelisis, etc.</td>
<td>Insert urinary catheter to relieve bladder obstruction</td>
</tr>
<tr>
<td>Monitor creatinine, BUN, electrolytes, urinary</td>
<td>Treat fluid and electrolyte abnormalities as needed. Insert urinary</td>
</tr>
<tr>
<td>output</td>
<td>catheter to follow output.</td>
</tr>
<tr>
<td>Look for life-threatening complications of</td>
<td>Start renal replacement therapy (dialysis) for life-threatening</td>
</tr>
<tr>
<td>AKI: hyperkalemia, fluid overload, CNS uremic</td>
<td>complications. Temporizing measures can be tried pending dialysis:</td>
</tr>
<tr>
<td>symptoms, metabolic acidosis, pericarditis</td>
<td>Hyperkalemia: calcium, NaHCO$_3$, insulin + glucose, albuterol,</td>
</tr>
<tr>
<td></td>
<td>kayexalate?</td>
</tr>
<tr>
<td></td>
<td>Fluid overload: vasodilators, furosemide</td>
</tr>
<tr>
<td></td>
<td>Acidosis: NaHCO$_3$</td>
</tr>
<tr>
<td></td>
<td>Pericardiocentesis or window for tamponade</td>
</tr>
</tbody>
</table>

Abbreviation: DC, discontinue.

CONCLUDING REMARKS

Older patients are at high risk for renal and electrolyte emergencies. Practitioners who take care of the geriatric patients must know how to evaluate for and manage these emergencies, including AKI, hyponatremia, hypernatremia, and hypercalcemia.

REFERENCES

RENAL AGING


HYPONATREMIA


HYPERNATREMIA


HYPERCALCEMIA


**ACUTE RENAL FAILURE**


