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AHC Media

Hyponatremia in the Emergency Department

Introduction

Sodium and water balance are closely linked, and abnormalities in one often occur in association with abnormalities in the other. Hyponatremia and disordered water balance are among the most common electrolyte disturbances seen in the emergency department (ED). Given the human body's remarkable adaptive capabilities, severe irregularities in sodium and water balance may be tolerated with surprisingly few symptoms, whereas rapid changes in sodium concentration, including the emergency physician's attempts to correct hyponatremia, may result in life-threatening illness. It is imperative that emergency physicians (EPs) and providers be versed in the recognition and management of hyponatremia and how it fits into the body's management of sodium and water balance. This article will review water balance and sodium, the epidemiology of hyponatremia, the clinical conditions associated with hyponatremia and their treatment, as well as preventive strategies to avoid sodium imbalance.

Note: 1 mEq/L = 1 mmol/L of sodium. The two are used interchangeably throughout this monograph.

Background: Water Balance

Total body water accounts for approximately 60% of total body weight in adults, although this figure varies based on age and gender.[1] Of this 60%, approximately 40% is intracellular fluid and 20% is extracellular fluid. Within the extracellular fluid, approximately two-thirds (or 15% of total body weight) resides in the interstitial space and one-third (or 5% of the total body weight) resides in the intravascular space. The primary electrolyte of the extracellular fluid is sodium. Proper fluid balance in the healthy adult requires an input of approximately 1 to 3 liters of water per day, replacing fluid lost through urine output, insensible loss (respiratory tract, skin, and feces), and sweat. Excessive loss due to fever, heavy sweating from exertion, or diarrhea increases water replacement needs. Water is able to diffuse between the intracellular and extracellular spaces via sodium and potassium transport channels, maintaining a relatively constant osmolality.

Maintenance of water balance requires normally functioning kidneys, urea production, intact thirst mechanism, and suppression of vasopressin (herein referred to as antidiuretic hormone or ADH) when serum sodium levels start to drop. In healthy individuals, the kidneys will excrete or resorb water to maintain a normal osmolality. ADH, secreted by the posterior pituitary gland, acts on the renal collecting system to increase reabsorption of water, increase

EXECUTIVE SUMMARY

- Hyponatremia is defined as a sodium of < 135 mEq/L. Note that 1 mEq/L = 1 mmol/L of sodium. Symptoms depend on the level of sodium as well as the rapidity of the drop.
- While mild cognitive changes leading to falls can be seen with mild hyponatremia, especially in the elderly, severe hyponatremia can lead to seizure, confusion, and cerebral edema.
- Correction of severe, acute, symptomatic hyponatremia may involve the use of hypertonic saline. However, patients with chronic hyponatremia require a slow correction of 6-8 mmol/L per 24 hours.
- Rapid or over correction in patients with chronic hyponatremia is associated with the development of osmotic demyelination syndrome.

urine concentration, and decrease urine output (i.e., anti-diuresis). This retention of free water has the effect of decreasing serum osmolality and sodium concentration. Ordinarily, a serum sodium level less than 135 mEq/L should trigger suppression of ADH, with resultant diuresis of dilute urine. Hyponatremia can develop if more water is ingested than can be secreted by the kidneys, or if the ability of the kidneys to provide effective diuresis of dilute urine is compromised by kidney disease, diuretics, or abnormal presence of ADH. In addition, lack of dietary protein can result in hyponatremia, as decreased excretion of urea limits water excretion, even in cases of profoundly low urine osmolality. An intact thirst mechanism provides stimulus to increase the amount of water consumed when serum osmolality increases, preventing dehydration and the development of hypernatremia.[2]

Hyponatremia Defined

Hyponatremia is defined as a serum sodium level of less than 135 mEq/L. Hyponatremia may be further classified as mild (135-125 mEq/L) or severe (less than 125 mEq/L). Severity of the symptoms is dependent both on the serum sodium concentration as well as the rapidity of change. Acute and severe hyponatremia may result in cerebral edema, seizures, coma, and cardiopulmonary arrest, but even chronic mild hyponatremia is associated with poor outcomes. These patients may have subtle neurocognitive deficits that are difficult to detect, and resolve with correction of the hyponatremia. These deficits put individuals at risk for falls and traumatic injury. Patients with even mild hyponatremia have a 30% higher risk of death and are hospitalized 14% longer than those with a normal serum sodium. This increased mortality risk occurs in commonly observed clinical conditions across large numbers of patients, including those with myocardial infarction, heart failure, and pulmonary infections.[3,4] Even mild abnormalities in sodium among patients in the ICU is an independent predictor for mortality.[5]

Epidemiology and At-risk Populations

Hyponatremia is the most common electrolyte disorder encountered in clinical medicine. The prevalence of hyponatremia in the United States ranges from 3 million to 6 million individuals per year. Approximately 3-6% of adult patients in the ED have some degree of hyponatremia, and the reported incidence of hospital-associated hyponatremia ranges between 10% and 30%, depending on the patient population, with severe hyponatremia accounting for 1% of patients. As previously noted, hyponatremic patients have an increased risk of death and longer hospital stays than patients with normal serum sodium levels; overall mortality of hyponatremia ranges from 3% to 29%. The leading causes of hyponatremia in ED patients are diuretic use and syndrome of inappropriate antidiuretic hormone secretion (SIADH).[1,2,6]

To identify those with hyponatremia, as well as to institute preventive measures, it is first necessary to identify at-risk populations. In patients with no underlying kidney disease, the most common cause of hyponatremia is excessive intake of free water before, during, and after endurance events. This most commonly occurs during sustained, high-intensity endurance activities such as marathons or triathlons.[7] "Blanket" hydration advice in which one recommendation fits all has led to overdrinking by well-meaning athletes.[8] They will typically consume more fluid than they lose in sweat, and may actually gain weight over the course of an event. As the event proceeds, the athlete may develop lethargy and nausea secondary to low sodium. These symptoms may inadvertently be taken as signs of dehydration, prompting even greater fluid intake.[9] Some degree of hyponatremia may occur in as many as 2-7% of participants.[10] Most cases lead to little or no complications and may be treated with close monitoring and fluid restriction. Mentally ill patients may rapidly consume large amounts of water and become hyponatremic. Individuals who consume large quantities of fluid but little protein may also become hyponatremic, due to limited free water excretion in the setting of low urea levels.

Secretion of ADH (with resultant limiting of free water excretion) in spite of low plasma sodium concentration can occur in the setting of hypovolemia, heart failure, or liver disease. SIADH occurs when ADH continues to be released without an osmotic or hemodynamic stimulus. ADH may be released in response to pain, stress, or hypoxia. Other causes of SIADH include malignancy, pulmonary disease, and central nervous system (CNS) trauma, infection, or ischemia.[1] In hospitalized patients, the risk of SIADH is highest among the elderly, postoperative patients, those in the ICU, and those with CNS disorders.[2]

Diuretic medications used for the treatment of hypertension or for control of peripheral edema enhance fluid loss but also impair the kidney's ability to excrete dilute urine. The end result is excess sodium loss through the urine with resultant hyponatremia. Thiazide

diuretics carry the greatest risk for development of hyponatremia, as well as increased hyponatremia severity; this risk increases with duration of use.[6] Thiazide diuretics are often prescribed as first-line therapy for hypertension in elderly patients, so the EP should consider hyponatremia as a cause of even subtle neurological complaints in older patients taking these medications.

Other than diuretics, there are dozens of drugs that affect water homeostasis and may result in hyponatremia. The most common non-diuretic medications associated with development of hyponatremia include antidepressants (tricyclics, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors [SSRIs]) and antipsychotics (phenothiazines and butyrophenones). SSRIs cause hyponatremia more frequently than other antidepressants; hyponatremia may develop in up to 30% of patients, usually within the first two weeks of treatment. Elderly patients and those taking thiazide diuretics are at greatest risk. The mechanism is believed to be medication-induced increases in central ADH secretion.[11] Antiepileptics (carbamazepine and valproic acid) and opioid analgesics are associated with the development of hyponatremia via the same mechanism. Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease water secretion by potentiating the effects of ADH, and are associated with development of hyponatremia in patients with preexisting SIADH (discussed below). NSAID use by marathon and ultramarathon runners is also associated with hyponatremia, although this may be confounded by other factors such as overconsumption of free water resulting in decreased serum sodium concentrations.

The use of 3, 4-methylenedioxymethylamphetamine (MDMA, ecstasy, XTC, E, X, rolls, beans, Adam, Molly) has been associated with development of hyponatremia. Direct stimulation of ADH secretion by MDMA and its metabolites results in dilutional hyponatremia; excess water intake to counter hypothermia is common in MDMA and is likely a contributing factor.[11,12] Females appear to be at greater risk for development of severe hyponatremia; instances of coma, seizure, rhabdomyolysis, and death have occurred. In patients with a history of recent MDMA use, even mild head injury has resulted in development of severe hyponatremia.[13,14,15,16]

Hospital-acquired hyponatremia is the most common cause of hyponatremia in children.[17] Children younger than 16 years, those with hypoxia, and those with any acute neurologic injury or infection are also at risk for development of hyponatremia. As in adults, ADH levels are increased in hospitalized patients secondary to pain, stress, hypoxia, and administration of certain medications. Administration of hypotonic maintenance fluids in the setting of increased ADH levels may result in free water retention and hyponatremia. Children in the postoperative setting appear to be at the greatest risk;[18] multiple nonosmotic stimuli for ADH production, such as subclinical volume depletion, pain, stress, nausea and vomiting, narcotic use, and third spacing, may lead to hyponatremia, especially if hypotonic fluids are administered. Because of a higher ratio of brain to intracranial volume, prepubescent children may be at higher risk for the development of cerebral edema and encephalopathy. Volume regulation of brain cells is impaired in patients with brain injury, and the movement of additional water into the brain as a result of even mild hyponatremia can result in herniation and death. Hypoxic brain injury, as well as CNS infection, abscess, or tumor, may result in SIADH and hyponatremia.

Hyponatremia can occur in spite of suppression of ADH release in a number of clinical conditions. These include overdrinking (by athletes and in primary polydipsia), advanced renal failure, and low dietary solute intake (such as beer potomania or tea and toast diet). These conditions are each discussed further below.

Presenting Signs and Symptoms

Often the manifestations of hyponatremia are subtle, becoming more noticeable when the changes are large or rapid.[19] A recent study evaluating patients with hyponatremia in the ED found that the most common presentation was neurologic symptoms (21%) such as dysarthria, motor function deficits, sensory loss, vertigo, balance disorder, and headache, followed by fatigue (19%), abdominal pain (11%), and dyspnea (8%). More severe neurologic symptoms included seizures and coma (9%), and confusion (6%).[6] Other common presenting symptoms include muscle weakness, nausea, vomiting, disorientation, depressed reflexes, irritability, and tachypnea. Most patients will develop symptoms with serum sodium less than 125 mmol/L. Both patients with extremely low serum sodium and those with an acute decrease in serum sodium are at greatest risk for acute deterioration secondary to cerebral edema.[20] These patients may present with or develop seizures, coma, respiratory arrest, and brain-stem herniation. It is important to mention that although some patients may appear asymptomatic, studies suggest they often have some degree of cognitive impairment, specifically with concentration. When even mild hyponatremia is treated, cognition often improves.[20,22] Hyponatremia is also associated with osteoporosis and unsteady gait, greatly increasing the rate of falls and fractures, which is an important cause of morbidity and mortality in elderly patients.[21,22]

Clinical Conditions Associated with Hyponatremia

Determining the underlying cause of hyponatremia is important, as it will direct therapy. The initial assessment of the patient with hyponatremia should include measurement of serum osmolality and urine sodium as well as clinical determination of the patient's volume status. The serum osmolality should be examined first to determine if the hyponatremia is isotonic, hypertonic, or hypotonic. Isotonic hyponatremia is also termed pseudohyponatremia, as it is most often due to severe hypertriglyceridemia or hyperproteinemia. The excessive serum concentrations of lipids or proteins interfere with the measurement of sodium and result in falsely low numbers. Hypertonic hyponatremia (serum Osm > 295 mOsm/kg H_2O) is usually due to the presence of other

Table 1. Hyponatremia Types and Causes

Hypovolemic Hyponatremia

- Gastrointestinal loss (vomiting, diarrhea)
- Renal loss (diuretic therapy, adrenal insufficiency)

Euvolemic Hyponatremia

- SIADH (secondary to neoplastic disease, CNS disorders, drugs, etc.)
- Glucocorticoid insufficiency (pituitary disorders)
- Overdrinking (endurance athletes, primary polydipsia, beer potomania)

Hypervolemic Hyponatremia

- Congestive heart failure
- Chronic kidney disease
- Nephrotic syndrome

serum osmolytes. The most common scenario is the patient with significant hyperglycemia in diabetic ketoacidosis. In these cases, the sodium typically normalizes with insulin administration and reduction in the serum glucose. Hypertonic hyponatremia also may be seen with administration of IV mannitol in patients with elevated intracranial pressure. Hypotonic hyponatremia (serum Osm < 275 mOsm/kg H_2O) is the common subtype of hyponatremia seen in the ED. Given the broad differential for hypotonic hyponatremia, it is helpful to further characterize it based on volume status into hypovolemic, euvolemic, and hypervolemic hyponatremia. (*See Table 1.*)

Hypovolemic Hyponatremia. Hypovolemic hyponatremia is the most common subtype of hypotonic hyponatremia encountered in the ED.[6] Because volume depletion cannot be tested directly, clinicians must use a combination of history, physical exam, and laboratory data to determine if a patient is hypovolemic. If clinical assessment of volume status is unclear and the patient is stable, one approach that is both diagnostic and therapeutic is to give a 0.5 to 1 L bolus of 0.9% NaCl to see if the hyponatremia will begin to correct itself as euvolemia is restored.[21] In patients who appear volume depleted, hyponatremia is usually secondary to either renal or gastrointestinal loss of sodium and water. Obtaining a urine sodium can aid in differentiating renal losses from extrarenal losses. Urine sodium less than 10 mmol/L suggests extrarenal losses, usually from vomiting and diarrhea. Urine sodium greater than 20 mmol/L suggests renal losses. The most common cause of renal sodium loss is diuretic therapy, and thiazides are the primary culprits. As noted earlier, they remain one of the most common causes of hyponatremia in the ED. Less common causes of medication-related renal sodium loss include loop diuretics and angiotensin-converting enzyme inhibitors. One other potential cause of hypovolemic hyponatremia is mineralocorticoid deficiency from primary adrenal insufficiency. In this instance, the lack of aldosterone results in renal salt wasting and hypovolemia. This stimulates release of ADH, which results in retention of free water and hyponatremia.

Euvolemic Hyponatremia. Hyponatremic patients with no clinical evidence of volume depletion (i.e., no orthostatic hypotension, normal skin turgor, moist mucosa) and no evidence of volume overload (i.e., edema, ascites) should be considered euvolemic. In these patients, hyponatremia is almost always the result of inappropriate ADH secretion and the resulting relative excess of body water. SIADH is the most common cause of euvolemic hyponatremia and a common cause of hyponatremia in the ED.[6] Laboratory features include low serum osmolality with inappropriately elevated urine osmolality (Uosm > 100), elevated urine sodium (> 20-30 mmol/L), and normal kidney function. SIADH is associated with a wide variety of disorders, the most common of which include neoplastic disease (small cell lung cancer, mesothelioma, pancreatic cancer, lymphoma), CNS disorders (mass lesions, encephalitis, meningitis, Guillain-Barre), drugs (narcotics, carbamazepine, MDMA, SSRIs, antineoplastics), and pulmonary disease (infections, asthma, chronic obstructive pulmonary disease).[2] It is important to remember that SIADH is a diagnosis of exclusion, so all other causes of hyponatremia must be ruled out.

Another potential cause of euvolemic hyponatremia is glucocorticoid deficiency in patients with pituitary disorders. Here, a deficiency of cortisol results in failure to suppress ADH secretion. Euvolemic hyponatremia also may be seen in endurance athletes who have excessive fluid intake in the presence of increased ADH secretion. There are additional causes of euvolemic hyponatremia that are not related to ADH secretion. In primary polydipsia, abnormal thirst regulation results in excess water consumption; the mechanism by which this occurs is not clear. Most patients with primary polydipsia have psychiatric disease (such as acute psychosis with schizophrenia), hence the sometimes-used term "psychogenic polydipsia." Hyponatremia can develop following water consumption that exceeds the kidneys' ability to secrete such large volumes.[2] Chronically malnourished patients who consume large volumes of fluid but little protein may develop hyponatremia. Alcoholics who consume large volumes of beer at the expense of other nutrition (beer potomania) or individuals on a high water/low protein diet (such as a "tea and toast" diet in elderly patients who can no longer prepare meals for themselves) are at risk.[2,21] The decreased protein intake and subsequent lack of urea impairs free water secretion, compounding the problem of high fluid consumption and resultant hyponatremia.

Hypervolemic Hyponatremia. Hypervolemic hyponatremia occurs when the water retention exceeds sodium retention. Common causes include heart failure, cirrhosis, chronic kidney disease (CKD), and nephrotic

Table 2. Hyponatremia At-risk Populations

Endurance Athletes

- Excessive fluid intake that exceeds fluid loss in endurance events may lead to acute hyponatremia.
- Physicians, coaches, trainers, and the athlete should be educated on recognition and prevention.
- Avoid drinking on schedule; instead drink ad libitum (i.e., when thirsty).

Elderly

- Disease states (congestive heart failure, chronic kidney disease) and medications (thiazide diuretics, antidepressants) put elderly at risk.
- Use caution when prescribing medications for elderly; arrange follow-up exam and testing if you start an elderly patient on a new medication in the emergency department.

Children

- Avoid hypotonic fluids for children treated in the ED or admitted to the hospital.
- MDMA use in teenagers and young adults is associated with potentially fatal hyponatremia.

syndrome. In heart failure, decreased cardiac output is sensed by the aortic and carotid baroreceptors. This triggers an increase in adrenergic activity, renin release, and secretion of ADH. The secretion of ADH results in water retention and hyponatremia.[21] Patients with liver failure may also present with hypervolemic hyponatremia, but generally only when accompanied by third spacing due to ascites.[23] Decreased intravascular volume with cardiac under-filling leads to activation of the renin-angiotensin-aldosterone system and again, release of ADH. Overall, these mechanisms cause renal vasoconstriction and water retention.

In CKD, patients with significantly impaired glomerular filtration rates have damaged nephrons that are less able to dilute urine despite appropriate suppression of ADH. The result is concentrated urine and free water retention. Water intake that exceeds urine output and insensible losses can cause hyponatremia. Patients may appear euvolemic or, if they retain salt and develop edema, hypervolemic. Significant proteinuria in nephrotic syndrome is far less common than the above entities but may result in hyponatremia. When renal protein loss causes serum albumin to drop below 2 g/dL, intravascular volume loss ensues, and decreased pressure at the baroreceptor ultimately can cause increased release of ADH and free water retention.

Treatment of Hyponatremia

The treatment of hyponatremia varies and depends on multiple factors, including the underlying cause and fluid status, severity of the presenting symptoms, and the time course over which the disease process has developed. The EP must often take all these factors into account simultaneously while evaluating a hyponatremic patient in the ED.

Acute Hyponatremia. Acute hyponatremia is generally estimated to have developed in less than 48 hours. Causes of acute hyponatremia include MDMA and other drugs, large gastrointestinal diuresis such as colonoscopy preparation, and endurance exercise with inadequate or excessive fluid consumption. In acute hyponatremia, patients are at increased risk for brain herniation due to cellular swelling in a closed space. Within 24-48 hours, the brain is able to compensate for the osmolality difference between the extracellular and intracellular spaces by exuding solutes; however, in acute hyponatremia, the osmolality difference leads to cellular swelling. These patients may present with severe neurologic symptoms and ultimately develop brain herniation.[24] Patients with acute hyponatremia require rapid intervention. Although many of these patients will have mild symptoms such as headache, nausea, vomiting, or confusion, their clinical course can deteriorate rapidly to altered mental status, seizures, respiratory arrest, herniation, and even death. The EP should confirm that the serum sodium was drawn appropriately and in the same manner as any previous values, if available. Any factors contributing to hyponatremia should be addressed and any cause-specific therapies should be initiated. Based on present literature, most patients will have significant improvement or reversal of symptoms with an increase of 4-6 mmol/L in the serum sodium.[25] Current guidelines recommend a 100-150 mL bolus of 3% hypertonic saline over 10-20 minutes, with repeat doses up to two times as needed for patients with acute symptomatic hyponatremia.[2,3,20,26,27] Additional guidelines recommend somewhat less aggressive therapy for patients with mild to moderate symptoms, such as nausea, vomiting, or mild confusion, as they are less likely to develop cerebral edema. These patients should receive 3% hypertonic saline at a rate of 0.5-2 mL/kg/h. The goal of hypertonic saline is not to achieve a specific number, but rather to alleviate any significant symptoms. Once the symptoms improve, hypertonic saline can be discontinued. Recheck sodium at the one-hour mark to avoid overcorrection (see "Overcorrection" section below). (*See Table 3.*) At this time, the patient will require admission for continued therapy and repeat serum sodium every four hours.[2,20] Further treatment will depend on the underlying cause, as discussed below.

Chronic Symptomatic Hyponatremia. The treatment of chronic hyponatremia is more complex and requires greater attention to the rate of correction. Rapid correction of chronic hyponatremia is associated with cerebral edema and increased intracranial pressure, leading to central nervous system damage such as osmotic demyelination syndrome, which may be devastating. Multiple guidelines exist for the rate of correction for chronic

Table 3. Hyponatremia Treatment Recommendations

Acute Hyponatremia

- Severe Symptoms (seizure, coma)
  - 100-150 mL bolus of 3% hypertonic saline over 10-20 minutes
  - May repeat for total of 3 doses
- Moderate Symptoms (confusion, nausea and vomiting, severe headache)
  - 3% hypertonic saline at a rate of 0.5-2 mL/kg/h
  - Recheck at 1- and 4-hour mark
  - Goal is symptom resolution/improvement

Chronic Symptomatic Hyponatremia

- Severe Symptoms (seizure, coma)
  - 150 mL bolus of 3% hypertonic saline given over 10-20 minutes
  - Repeat x 1 if necessary
  - Correction goal of 5 mEq/L improvement
  - Avoid overcorrection
- Moderate Symptoms (confusion, nausea and vomiting, severe headache)
  - Single 150 mL bolus 3% hypertonic saline
  - Remove precipitating factors (excess fluids, medications, etc.)
  - Avoid overcorrection (increase > 10 mEq/L over 24 hr)

Asymptomatic Hyponatremia

- Remove precipitating factors (excess fluids, medications, etc.)
- Monitor sodium every 6 hours
- Avoid overcorrection (increase > 10 mEq/L over 24 hr)

hyponatremia. Historically, the widely accepted rate of change was less than 25 mmol/L sodium in 48 hours. Current recommendations are highly variable, but, in general, recommend an even more conservative approach in chronic hyponatremia.[3,28,29] A correction rate of 6 mmol/L/day has been found to sufficiently treat severe symptoms without creating the complications of overcorrection. This must be balanced with the inherent risks associated with hyponatremia: rates of change less than 3-4 mEq/L/24 hours are associated with increased mortality.[30] Current guidelines strike a good compromise: a rate of 6-8 mmol/L per 24-hour period and any subsequent 24-hour period. Additional recent European guidelines suggest a similar rate of 10 mEq/L in the first 24 hours and 8 mmol/L for any subsequent 24-hour period. These rates are agreed upon in patients with both symptomatic and asymptomatic hyponatremia.[21,31]

Patients with chronic hyponatremia who develop severe symptoms require acute intervention with hypertonic saline. Severe symptoms most often include focal neurologic deficits, altered mental status, seizures, and coma, but severe vomiting and abnormal and deep somnolence also may prompt treatment with hypertonic saline. Three percent hypertonic saline is given at an infusion of 150 mL over 20 minutes. If necessary, after rechecking the serum sodium, an additional bolus may be given with a target serum sodium increase of 5 mEq/L. At this point, 0.9% normal saline (NS) should replace the hypertonic saline while the clinician investigates the cause in order to initiate cause-specific therapy. Serum sodium should be checked following any bolus of hypertonic saline, and then every 6 hours until normalization.[2,31]

In the patient with moderately severe symptoms, clinical guidelines recommend a single 150 mL infusion of 3% hypertonic saline given over 20 minutes with a goal of 5 mEq/L in the first 24 hours. Moderately severe symptoms include severe nausea without vomiting, headache, and confusion.[31] Although mortality is less among these patients, rapid decompensation can still occur. They should be admitted to the hospital, and serum sodium should be carefully monitored.

Asymptomatic Hyponatremia. In asymptomatic or mildly and moderately symptomatic hyponatremia, treatment depends on the patient's fluid status. Similar to other patient groups, the goals of sodium correction in asymptomatic hyponatremia are 6-8 mEq/L (with an absolute maximum of 10 mEq/L) in the first 24 hours, given the risk of overcorrection, with the serum sodium being rechecked every 6 hours.[21]

Directed therapy for the underlying causes of hyponatremia applies to both acute and chronic hyponatremia. Once symptoms have begun to improve or resolve, therapy is tailored based on the patient's volume status. For patients with hypovolemic hyponatremia, the goal is intravascular repletion with fluid resuscitation and removal of precipitants. Common causes of low volume hyponatremia are gastrointestinal fluid losses, diuretic use, and mineralocorticoid deficiency. With volume repletion, ADH will decrease, allowing for decreased uptake of free water and normalization of plasma sodium. Fluid resuscitation starts with isotonic fluids, generally 0.9% NS at a rate of 0.5-1.0 mL/kg per hour. However, in patients with hemodynamic instability, fluid resuscitation supersedes strict adherence to a controlled rate of correction.[21,31] Fluids may be altered to reverse accompanying electrolyte or base deficits, but the clinician must recall that administration of potassium will increase the serum sodium due to cellular exchange of potassium and sodium, which may increase sodium more quickly than desired. The clinician should reevaluate the serum sodium when the patient becomes clinically euvolemic and/or every 6-8 hours. In patients with otherwise normal renal function, the serum sodium should correct slowly; however, in cases of renal impairment, the kidney may undergo free water excretion, potentially causing a correction that is too rapid. Once the goal of correction is met, the clinician may use 0.45% NS or D5W.[1,21,31] When a mineralocorticoid deficiency is suspected, the patient should receive a glucocorticoid, such as

50-100 mg of hydrocortisone IV every 8 hours. Mineralocorticoid deficiency that leads to volume depletion is often severe and will require supplementation of both mineralocorticoid and glucocorticoid; however, in the acute setting, hydrocortisone is sufficient.[21]

Treatment of euvolemic hyponatremia is again tailored to the specific cause. In SIADH, the patient generally responds to improvement of the underlying cause, such as treatment of pneumonia.[32] However, in moderate or profound hyponatremia, fluid restriction without salt restriction is considered first-line therapy. These patients may benefit from 0.25-0.5 g/day of urea or oral salt tablets with low-dose loop diuretic to increase serum solute concentration.[21] All patients with concern for SIADH should be evaluated for glucocorticoid deficiency. In patients with suspected primary or secondary adrenal insufficiency, glucocorticoids should be administered after the initial blood draw. Patients may receive a stress dose or maintenance dose of steroids, as in mineralocorticoid deficiency. Replacement of glucocorticoids often causes rapid free water loss, leading to rapid change in serum sodium. Finally, patients with primary polydipsia most often require only fluid restriction. Current clinical guidelines no longer recommend lithium and demeclocycline. Lithium and demeclocycline cause polyuria and nephrogenic diabetes insipidus as a side effect and do improve hyponatremia; however, both are associated with azotemia and acute renal injury.[19,21,33]

Patients with hypervolemic hyponatremia require treatment of the underlying disease leading to hyponatremia and often will require fluid restriction. The most common causes include heart failure, nephrotic syndrome, and cirrhosis with concomitant ascites. Most often, patients with these syndromes receive a fluid restriction of 0.8 L/day.[21] The body normally has an obligatory fluid loss of > 1.0 L/day from urinary excretion and insensible losses, so the patient will have a negative fluid balance and increased serum sodium concentration. Unfortunately, this process is slow and understandably difficult for some patients, and different strategies may be helpful. In patients with congestive heart failure (CHF), loop diuretics generally increase water loss, leading to an improved serum sodium in a more timely fashion than fluid restriction alone.[34,35] Cirrhosis with ascites can be treated with water and salt restriction, paracentesis, diuretics, and albumin. However, it is important to note that the evidence for fluid restriction in cirrhosis is lacking, and these patients can be very difficult to treat. Nephrotic syndrome is treated similarly to chronic kidney disease with water and salt restriction and diuretics, but may also benefit from albumin with diuretics.[2,32,36]

EPs should become familiar with vaptans, which are additional agents used to treat hyponatremia. Controversy exists regarding the indications for and efficacy of these medications. Vaptans are antagonists to the vasopressin V1A, V1B, and V2 receptors, which ultimately cause free water loss by blocking the action of ADH; this leads to an increased serum sodium concentration.[37] Conivaptan and tolvaptan are the most commonly used vaptans and both are FDA-approved for the inpatient treatment of euvolemic hyponatremia. Generally, these are reserved for severe hyponatremia (value < 125 mEq/L) or for those who do not respond to fluid restriction in the case of hypervolemic and euvolemic hyponatremia. Examples include individuals with recalcitrant SIADH, CHF, or cirrhosis.[21,31,34,35,36,38] Although in some studies vaptans seem to normalize sodium more quickly, they are expensive and the safety of their use is not clear. Risks include overcorrection and nephrotoxicity, especially in patients with cirrhosis. Vaptans have not been well-studied in the ED setting nor for treatment of acute hyponatremia, and clinical experience in the ED is limited. The EP can consider the use of vaptans in appropriate patient populations, but should obtain close consultation with a nephrologist or endocrinologist.[1,20,36,39]

Overcorrection

When treating any patient for hyponatremia, the EP must pay close attention to overcorrection, which is considered a medical emergency. Although serious complications are rare, occurring in less than 2% of cases, they can be devastating, resulting in significant neurologic disability or death.[40,41] Many patients already will be admitted before serial serum sodium levels return, but in this current era of overcrowded EDs and boarding, the EP must be aware of consequences of overcorrection and understand when to intervene.

Osmotic Demyelination. Osmotic demyelination syndrome (ODS) refers to central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) and is a commonly discussed consequence of overzealous correction of hyponatremia. ODS occurs in 1-10% of patients undergoing treatment for hyponatremia.[42,43] Adams et al initially recognized ODS on an autopsy in the 1950s; in the 1970s, Tomlinson suggested it was due to a metabolic derangement, and finally the connection to rapid correction of hyponatremia was established. However, it was not until the late 1980s that Sterns et al created the term ODS after recognizing a biphasic pattern following rapid overcorrection of chronic hyponatremia wherein the patient initially improves from the acute hyponatremic symptoms and then develops progressive neurologic symptoms 2-8 days later.[44,45] Animal studies also demonstrate that overcorrection of hyponatremia predictably leads to lesions visible on MRI consistent with ODS that are not present before correction. Although there are other factors associated with development of ODS, overcorrection of hyponatremia remains the most common.[46,47,48]

The mechanism of ODS is not clearly understood but likely is associated with osmolality differences and cellular edema. As previously mentioned, the brain adapts to chronic hyponatremia by extruding solutes; when the osmolality again changes with therapy, fluid shifts can cause cellular swelling. This edema, for unclear reasons, causes noninflammatory loss of myelin without disrupting the neuronal cell bodies and axons.[48,49,50] As the names imply, CPM predominantly affects the pons and EPM predominantly affects the cerebellum. Changes can be widespread; other parts of the brain affected in ODS include the geniculate body, external capsule, basal ganglia, thalamus, gray-white junction, and hippocampus.[44,48,51]

In classic biphasic ODS, the patient initially improves following treatment. This is followed by deterioration starting with corticobulbar symptoms (dysphagia and dysarthria), corticospinal tract symptoms (flaccid quadriparesis), basis pontis symptoms (spastic quadriparesis), and ultimately may progress to locked-in syndrome.[48] The diagnosis of ODS is generally clinical and confirmed by either autopsy or diffusion-weighted imaging (DWI), which is the most sensitive technique for visualization of demyelination.[48] Not all patients with overzealous correction develop ODS, and studies show that certain populations are at greater risk, including those with chronic alcoholism (more than half of cases), malnutrition, advanced liver disease, serum sodium < 105 mEq/L, and hypokalemia. Most cases seem to occur with rates of correction greater than 18 mEq/L/24 hr, but have been seen in rates as low as 10 mEq/L/24 hr and 21 mEq/L/48 hr. Both men and women and affected equally, and children are also susceptible.[52,53]

One group of patients unlikely to be at risk for ODS are those who have developed hyponatremia rapidly (within several hours) due to increased free water intake. These patients have not had time for the brain to adapt to the acute alterations in osmolality. This includes endurance athletes, people with primary polydipsia, and individuals who have used MDMA (in whom the issue of increased water intake is compounded by increased ADH secretion.) This lower risk of complicated overcorrection may in fact be a blessing, as these patients are also at the greatest risk for herniation.[53]

ODS can be debilitating, but complete recovery is possible. Before the use of DWI, ODS was thought to be irreversible; however, repeat images after treatment have shown complete resolution of signal abnormalities in up to 63% of patients.[52] Animal studies show that active reduction of serum sodium following overcorrection reduces rates of ODS.[54] Given the degree of potential harm that ODS can inflict, the EP must closely monitor the change in sodium and stop therapy and treat overcorrection when necessary.

Treatment for Overcorrection. Given the complexity of dysnatremias, it should come as no surprise that the desired rate of correction is often not met. Studies have found that as many as 49% of patients had non-optimal correction, with a total of 27% having overcorrected sodium at 24 hours.[43] Both persistent hyponatremia and rapid correction of hyponatremia pose risks for patients. While it is a difficult balance, we have noted earlier that increasing the serum sodium concentration by 4-6 mEq/L is enough to reverse symptoms of hyponatremia. This falls far below the rate of overcorrection. When overcorrection does occur, the clinician can employ recently established interventional guidelines.

Current clinical practice guidelines recommend intervention for correction rates that exceed 10 mEq/L in the first 24 hours or 8 mEq/L in any 24-hour period in patients with a starting serum sodium less than 120 mEq/L.[31] This is most critical in patients at risk for development of ODS (i.e., those most likely to have chronic hyponatremia.) When overcorrection occurs, stop current treatment and consult nephrology or endocrinology for recommendations on an electrolyte-free water infusion and to discuss the possible use of desmopressin, a synthetic analog of ADH. Its use has been advocated by some authors when the serum sodium rises to 6-8 mEq/L in the first 24 hours, which is actually short of the therapeutic maximum. For active reduction, the clinician can give 2-4 micrograms desmopressin every 8 hours intravenously with oral water or intravenous 5% dextrose given at 3 mL/kg/hr.[21] When these interventions are undertaken, the serum sodium should be checked hourly.

Summary of Treatment and Disposition

The general approach for treating patients with hyponatremia is based on the duration and severity of the hyponatremia and on the presence and severity of symptoms. Use hypertonic saline in patients with acute or chronic hyponatremia with moderate to severe symptoms. Hyponatremic patients who are asymptomatic or have only mild symptoms may be treated with fluid restriction, with or without loop diuretics and oral sodium chloride. Underlying disease states, such as CHF, cirrhosis, CKD, pneumonia, etc., should be addressed. Vasopressin receptor antagonists are occasionally used, but are associated with serious limitations.

Any patient undergoing treatment for hyponatremia requires close evaluation and frequent lab draws. This is important not only to monitor for symptomatic improvement or signs of herniation and deterioration, but also to track the rate of correction (and prevent overcorrection.) Most patients undergoing therapy for hyponatremia will require hospitalization. Depending on the severity and acuity of the hyponatremia and nursing requirements, admission to the intensive care unit may be required. Patients who have developed hyponatremia acutely (such as an overdrinking endurance athlete) who present with mild symptoms and respond to therapy may be considered for discharge from the ED with close follow-up.

Consultation

EPs should consult a nephrologist or endocrinologist as well as an intensivist when use of hypertonic saline or vaptans is contemplated, when the serum sodium is < 120 mEq/L, when the hyponatremia is acute, or if hyponatremia is accompanied by severe symptoms. Additionally, consultations should be considered when the cause of hyponatremia is unclear or if SIADH is suspected and appropriate management is uncertain.[2]

Prevention of Hyponatremia

Athletes. Clinicians need to be aware of the risks for hyponatremia among endurance athletes, and should encourage runners to drink only when they are thirsty. Athletes should monitor their body weight during times of frequent training or competition to ensure that they are neither losing weight (putting them at risk for volume depletion and exertional heat illness) nor gaining weight (putting them at risk for hyponatremia). Exertional hyponatremia may be mistaken for exertional heat stroke, syncope, or another entity. If suspicion exists for exertional heat stroke, an

accurate temperature (rectal, esophageal) must be obtained. Serum sodium should be rapidly assessed in any endurance athlete presenting with a history of altered mental status, diminished level of consciousness, excess water consumption, and a normal core temperature. Point-of-care testing of serum sodium should be made available in the medical tent of any large endurance event. Otherwise, obtain it as quickly as possible in the ED. Athletes and coaches should be educated about the fact that the key to prevention is moderate fluid consumption based on perceived need ("ad libitum") rather than on a rigid rule.[26]

Elderly. Age-related impairment of water excretion and increased exposure to drugs and diseases that affect water balance place the geriatric population at increased risk of hyponatremia. Even mild hyponatremia has been linked to falls, fractures, and cognitive decline. Elderly patients with congestive heart failure, cirrhosis, or pneumonia are at greatest risk; serum sodium levels should be checked in all hospitalized patients on admission, and even mild hyponatremia should be noted and addressed.

In elderly patients started on a thiazide diuretic, SSRI, or selective norepinephrine reuptake inhibitors, arrangements should be made to check serum sodium levels within 1-2 weeks of initiation of therapy. Thiazide diuretics should be used with extreme caution in elderly patients, and avoided in individuals with diminished protein intake or during acute illness. Hospitalized and institutionalized elderly patients are at great risk for hyponatremia; care should be taken to avoid administration of diuretics, hypotonic fluids, and low-sodium tube feeding in those with impaired water-excreting capacity.[2]

Emergency Department. Patients may present to the ED with hyponatremia as a consequence of hyper- or hypovolemia, or may be euvolemic patients transferred from institutionalized settings. As such, the EP must be cognizant of the many etiologies behind hyponatremia and of its insidious effects, especially on elderly patients.

As a general rule, EPs should not administer hypotonic fluids to patients at risk for hyponatremia, especially those at extremes of age. Administration of normal saline or Ringer's lactate should predominate for fluid resuscitation. As noted, elderly patients and those with CHF, cirrhosis, or pneumonia are at risk for hospital-acquired hyponatremia; this risk is even greater in those requiring ICU admission. Avoid hypotonic fluids and thiazide diuretics during the patient's ED treatment. In patients who are started on diuretics (especially thiazide diuretics) or antidepressants in the ED, the EP should ensure that follow-up testing of serum sodium levels is facilitated. Patients should be discharged with strict return precautions, including even subtle changes in mentation, balance, or strength.[1,2,6]

Pediatrics. Consider all pediatric patients who receive IV fluid administration to be at risk for hyponatremia. Children younger than 16 years of age and those with hypoxia are at particular risk. Close monitoring of the serum sodium level in any child with hypoxia or neurologic injury is indicated, as even mild hyponatremia is associated with poor outcomes. Hypotonic fluids are no longer recommended for use as maintenance or resuscitation fluids in the pediatric population due to the high risk of iatrogenic hyponatremia.[1]

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CME/CE Questions

1. A 57-year-old female presents to the ED with headache and nausea. She was recently diagnosed with lung cancer and started on chemotherapy. On presentation to the ED, she has serum sodium of 117 mEq/L. She is somewhat confused. A review of her medical record shows her serum sodium was 120 mEq/L at her appointment last week. On exam she is euvolemic. What is the best management of hyponatremia in this patient?
   A. Administer 100 mL hypertonic saline, up to three doses, until serum sodium returns to baseline.
   B. Give the patient an oral salt tablet, 20 mg of furosemide, and request fluid restriction.
   C. Administer a single 150 mL bolus of 3% hypertonic saline and admit her for observation.
   D. Administer a single bolus of NS and admit her for observation.
2. Following a 50K run, a 26-year-old female endurance athlete presented to the medical tent complaining of headache and nausea. Given concerns for dehydration, she was asked to drink a 32-ounce bottle of water. She did not improve and started to complain that her headache was worse, and she seemed slightly confused; EMS subsequently transported the patient to the ED. What is the most appropriate treatment for this patient?
   A. 16-ounce sports drink
   B. 5% dextrose solution
   C. Hypertonic saline
   D. Normal saline infusion and glucagon
3. A 50-year-old man weighing 70 kg presents to the ED with altered mental status and is found to have serum sodium 110 mEq/L. He is started on hypertonic saline and his

neurologic status begins to improve. As you continue to treat the patient and prepare for admission, the nurse calls you to the bedside and states that he is now more confused than before. Repeat serum sodium is 125 mEq. What is the most appropriate intervention?
   A. Stop hypertonic saline and start desmopressin 2 micrograms with D5W at 210 mL/hr.
   B. Stop hypertonic saline and check serum sodium every 2 hours.
   C. Start tolvaptan dosing every 1 hour with serum sodium checks every 1 hour.
   D. Stop hypertonic saline and start D5 ½ normal saline at 210 mL/hr with serum sodium checks every 1 hour.

4. A 70-year-old male presents to the ED after his primary care physician called him with an "abnormal lab result" on routine lab draws. He states "I think my sodium is too low." He is asymptomatic; the exam is unremarkable, and serum sodium is 115 mEq/L. What is the appropriate goal for correcting the serum sodium?
   A. Increase to 119 mEq/L in the first 24 hours and then to 123 mEq/L in the second 24 hours.
   B. Increase to 123 mEq/L in the first 24 hours and then to 131 mEq/L.
   C. No acute intervention is necessary at this time as the patient is asymptomatic and the cause of hyponatremia is unclear.
   D. Increase to 127 mEq/L in the first 24 hours and then to 139 mEq/L.

5. A 55-year-old female presents with a severe headache, nausea, and vomiting that started early that morning. She states that she was supposed to have a colonoscopy that morning but came to the ED because the headache was too severe. Serum electrolytes are significant for sodium on 121 mmol/L. What is the next best management of this patient?
   A. Redraw serum sodium and start the patient on normal saline.
   B. Check urine osmolality and urine sodium and start the patient on normal saline.
   C. Confirm appropriate lab draw and give the patient 100 mL of 3% hypertonic saline.
   D. Start normal saline IV, give Zofran 4 mg IV, and allow the patient to start oral rehydration.

6. What are the most common causes of hyponatremia in the ED?
   A. Congestive heart failure and diuretic use
   B. SIADH and gastrointestinal losses
   C. SIADH and diuretic use
   D. Gastrointestinal losses and congestive heart failure

7. Drugs associated with development of hyponatremia include which of the following?
   A. Thiazide diuretics
   B. SSRIs
   C. Carbamazepine
   D. All of the above

8. Hyponatremia may occur in spite of ADH suppression in all of the following e*xcept*:
   A. adrenal insufficiency.
   B. chronic kidney disease.
   C. primary polydipsia.
   D. both B and C.

9. Indications for use of vaptans in the ED include:
   A. an endurance athlete who presents with seizures and a serum sodium of 112 mEq/L.
   B. a hypervolemic patient with CHF and serum sodium of 120 mEq/L with poor response to fluid restriction.
   C. a hypervolemic patient with cirrhosis and serum sodium of 128 mEq/L with nausea and headache.
   D. both B and C.

10. Prevention of hyponatremia includes all of the following actions *except*:
   A. assuring follow-up when prescribing antidepressants for elderly patients.
   B. avoiding hypotonic fluids when treating children in the ED.
   C. increasing access to hydration stations at marathons.
   D. using NS or LR for fluid resuscitation in the ED.

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Hyponatremia in the Emergency Department

Hyponatremia Types and Causes

Hypovolemic Hyponatremia

- Gastrointestinal loss (vomiting, diarrhea)
- Renal loss (diuretic therapy, adrenal insufficiency)

Euvolemic Hyponatremia

- SIADH (secondary to neoplastic disease, CNS disorders, drugs, etc.)
- Glucocorticoid insufficiency (pituitary disorders)
- Overdrinking (endurance athletes, primary polydipsia, beer potomania)

Hypervolemic Hyponatremia

- Congestive heart failure
- Chronic kidney disease
- Nephrotic syndrome

Hyponatremia At-risk Populations

Endurance Athletes

- Excessive fluid intake that exceeds fluid loss in endurance events may lead to acute hyponatremia.
- Physicians, coaches, trainers, and the athlete should be educated on recognition and prevention.
- Avoid drinking on schedule; instead drink ad libitum (i.e., when thirsty).

Elderly

- Disease states (congestive heart failure, chronic kidney disease) and medications (thiazide diuretics, antidepressants) put elderly at risk.
- Use caution when prescribing medications for elderly; arrange follow-up exam and testing if you start an elderly patient on a new medication in the emergency department.

Children

- Avoid hypotonic fluids for children treated in the ED or admitted to the hospital.
- MDMA use in teenagers and young adults is associated with potentially fatal hyponatremia.

Hyponatremia Treatment Recommendations

Acute Hyponatremia

- Severe Symptoms (seizure, coma)
  - 100-150 mL bolus of 3% hypertonic saline over 10-20 minutes
  - May repeat for total of 3 doses
- Moderate Symptoms (confusion, nausea and vomiting, severe headache)
  - 3% hypertonic saline at a rate of 0.5-2 mL/kg/h
  - Recheck at 1- and 4-hour mark
  - Goal is symptom resolution/improvement

Chronic Symptomatic Hyponatremia

- Severe Symptoms (seizure, coma)
  - 150 mL bolus of 3% hypertonic saline given over 10-20 minutes
  - Repeat x 1 if necessary
  - Correction goal of 5 mEq/L improvement
  - Avoid overcorrection
- Moderate Symptoms (confusion, nausea and vomiting, severe headache)
  - Single 150 mL bolus 3% hypertonic saline
  - Remove precipitating factors (excess fluids, medications, etc.)
  - Avoid overcorrection (increase > 10 mEq/L over 24 hr)

Asymptomatic Hyponatremia

- Remove precipitating factors (excess fluids, medications, etc.)
- Monitor sodium every 6 hours
- Avoid overcorrection (increase > 10 mEq/L over 24 hr)

Supplement to *Emergency Medicine Reports*, January 15, 2016: "Hyponatremia in the Emergency Department." Authors: Brian L. Springer, MD, FACEP, Associate Professor, Wright State University, Department of Emergency Medicine, Dayton, OH; MacKenzie Gabler, MD, Resident Physician, Wright State University Emergency Medicine Residency Program, Dayton, OH.

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AHC Media

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an acute metabolic disorder characterized by markedly increased circulating ketone bodies leading to ketoacidosis in the presence of prolonged hyperglycemia due to an absence of insulin. DKA may present in subjects with Type 1 diabetes mellitus (T1DM) with an absolute or relative insulin deficiency or in patients with Type 2 diabetes mellitus (T2DM) due to relative insulin deficiency. DKA commonly occurs at the onset of T1DM but also may occur from withdrawal or omission of insulin therapy due to psychiatric, social, or economic reasons or due to increased insulin requirements during an acute illness.[1]

The use of continuous subcutaneous insulin infusion pumps using rapid-acting insulin also has been associated with a significant increase in incidence of DKA when compared to conventional therapy with multiple daily subcutaneous insulin injections.[2-15] The occurrence of DKA in patients using pumps is attributed to the exclusive presence of rapid-acting insulin in the pump, which, if interrupted, leaves no reservoir of basal insulin for blood glucose control, as well as to patients' reluctance in adjusting the basal rates and bolus dosages via pump in the presence of an acute illness. Moreover, pump failure may also occur due to occlusion of insulin pump infusion sets or inappropriate handling of the pump and lack of selection of an appropriate site (extensive scarring, lipoatrophy, or lipohypertrophy at the site).[5-15] DKA due to relative insulin deficiency occurs in T2DM, frequently at the onset of an acute disorder such as infection, trauma, myocardial infarction, congestive heart failure, and steroid therapy, as well as due to lack of appropriate dose adjustment in pregnancy and other conditions.[1] Finally, the FDA issued an advisory regarding the occurrence of DKA in subjects with T2DM following initiation of sodium/glucose cotransporter 2 (SGLT2) inhibitors.[16]

Epidemiology

Hospitalizations for DKA are increasing in the United States. A report by the Centers for Disease Control and Prevention analyzing data regarding hospital admissions between 1988 and 2009 in the United States describes a marked increase in the number of hospital discharges with DKA as the first listed diagnosis from 80,000 in 1988 to 140,000 in 2009.[17]

The age-adjusted hospital discharge rate for DKA per 10,000 overall population increased by 43.8% during this time period as well. The rise in the hospital discharge rate may be attributed to improved testing for diagnosis, availability of better management tools and protocols promoting improved survival, and an increase in the prevalence of diabetes over the period of analysis.[17] Thus, despite the rise per overall diabetic population, both the crude and age-adjusted hospital discharge rates for DKA per 1000 subjects with diabetes declined by 43.7% and 38.4%, respectively. Moreover, the age-adjusted hospital discharge rates

EXECUTIVE SUMMARY

- Diabetic ketoacidosis typically occurs at the onset of Type 1 diabetes mellitus, but also may occur from withdrawal or omission of insulin therapy in patients due to psychiatric, social, or economic reasons, as well as increased insulin requirements during acute illness.
- Patients on continuous subcutaneous insulin infusion pumps using rapid-acting insulin have an increased incidence of DKA.
- Patients with Type 2 diabetes mellitus have been reported to develop DKA with mild-to-moderate glucose elevations following initiation of sodium/glucose cotransporter 2 (SGLT2) inhibitors: canagliflozin, dapagliflozin, and empagliflozin.
- Initiate treatment with IV normal saline, 1 to 2 L over the first hour.
- Initiate IV insulin after initial fluid administration and after verifying serum potassium is above 3.3 mEq/L.
- Monitor serum glucose hourly with point-of-care testing for the initial 4 hours.
- Monitor and replace serum potassium during insulin infusion.

for diagnosis of DKA per 1000 subjects with diabetes declined among both men and women, as well as among whites and blacks, with a greater decrease among blacks than in whites (60.5% vs 45.0%).[17] Although clinicians often associate DKA with T1DM patients, DKA also occurs in T2DM patients, though not as frequently as in subjects with T1DM. In studies of first-time DKA, about 65-70% of patients have previously documented T1DM and about 30-35% are estimated to have T2DM.[18-23]

DKA is a serious and potentially life-threatening metabolic complication of diabetes mellitus, although mortality due to complications of DKA is rare in both children and adults. In 2009, the rate of mortality in patients presenting with hyperglycemia crisis (both DKA and hyperosmolar hyperglycemic non-ketotic syndrome) was reported to be 0.02% in patients with diabetes who were ≤ 45 years of age and 0.014% among older adults with diabetes.[24] Among children, cerebral edema was reported in 0.3-1% of DKA episodes and accounted for 57-87% of all DKA deaths.[25-27] Previously, elderly patients at extreme ages were at the greatest risk for complications from DKA, with increasing mortality with each passing decade.[28-34]

However, the mortality rate in the elderly has declined significantly recently due to the advent of newer insulin formulations; well-established management protocols with appropriate insulin administration (IV or IM); close monitoring of fluid status and metabolic parameters, including glycemia, serum electrolytes, and arterial blood gas; and markedly improved tools available for management of accompanying acute disorders.[31]

Pathogenesis

Insulin plays a major role in fuel homeostasis via its effects in the liver, muscle, and adipose tissue. Insulin promotes fuel storage in the liver by stimulation of glycogen synthesis and conversion of free fatty acids into triglyceride.[34,35] It also decreases fuel expenditure by inhibiting gluconeogenesis, glycogenolysis, and lipolysis, including triglyceride breakdown, resulting in a decline of circulating free fatty acids required as a substrate for ketogenesis (*see Figure 1*).[34-36] Glucagon is a counter-regulatory hormone with properties to oppose the effects of insulin on all fuel stores.[36] Insulin, free fatty acids, and ketones inhibit glucagon secretion, whereas amino acids, catecholamines, and cortisol stimulate its secretion. Glucagon stimulates hepatic glucose production by promoting both glycogen breakdown and gluconeogenesis. Additionally, other counter-regulatory hormones, such as catecholamines, cortisol, and growth hormones, complement the effects of glucagon on carbohydrate, protein, and lipid metabolism (*see Figure 2*).[34-36] Lack of insulin and increase in glucagon and other counter-regulatory hormones stimulate lipolysis and release free fatty acids, which are then converted to ketone bodies in the liver (*see Figure 3*).[34-36]

Acetoacetate and B-hydroxybutyrate are the two major ketone bodies produced by the liver during insulin deficiency and a rise in counter-regulatory hormones. Accumulation of these ketone bodies in the circulation accounts for the induction of anion gap metabolic acidosis (*see Figure 3*). Metabolic acidosis (pH < 7.2) stimulates the cerebral respiratory center, which in turn induces deep rapid respirations known as "Kussmaul" breathing, promoting respiratory alkalosis in an attempt to restore pH toward normal.[34-39]

Glucose is the most effective fuel for the normal functioning of all tissues. However, all organs and tissues require insulin for glucose entry, with the exception of the central nervous system, renal medulla, and red blood cells. Tissues are unable to utilize glucose during absolute or relative lack of insulin in T1DM and T2DM, especially in the presence of an acute disorder, and are forced to use ketones as an alternative source of energy.[34-36] Increased serum glucose concentration causes elevation in serum osmolality, leading to a shift of fluid from intracellular to extracellular compartment. Increase in osmolality stimulates the cerebral thirst center to increase fluid intake to help maintain both extra- and intravascular volumes. However, volume depletion and dehydration are exacerbated due to lack of fluid intake because of ketoacidosis-induced nausea and vomiting and lack of ability to communicate or ambulate in patients at extreme ages. Furthermore, fluid loss results in decreased renal blood flow, leading to diminished excretion of glucose, promoting greater rise in plasma glucose and, thus, osmolality.[37-39]

Patients with DKA may simultaneously manifest other acid-base disorders. The concurrent presence of other acid-base disorders is established

Figure 1. Pathogenesis of DKA

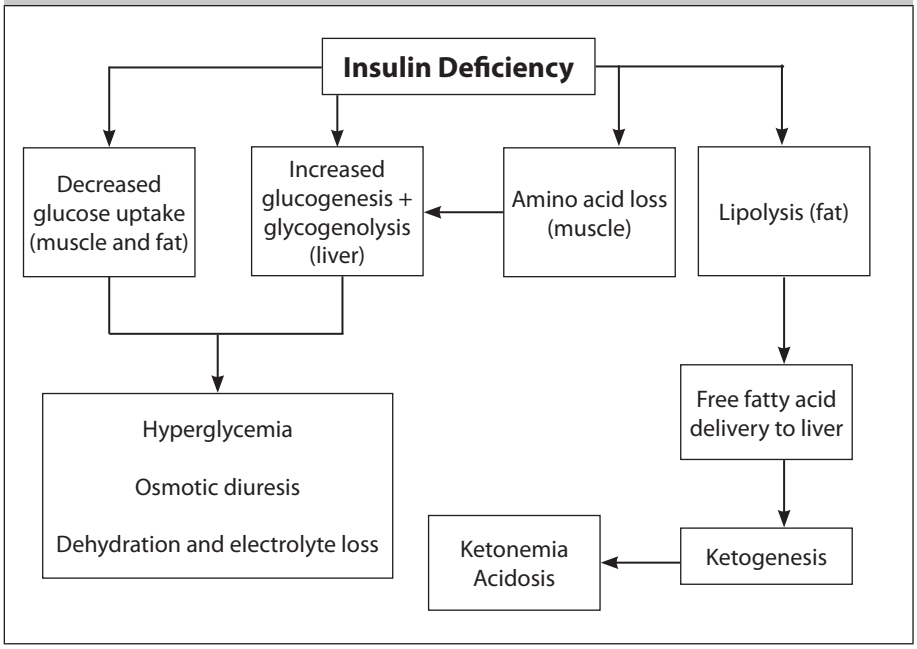
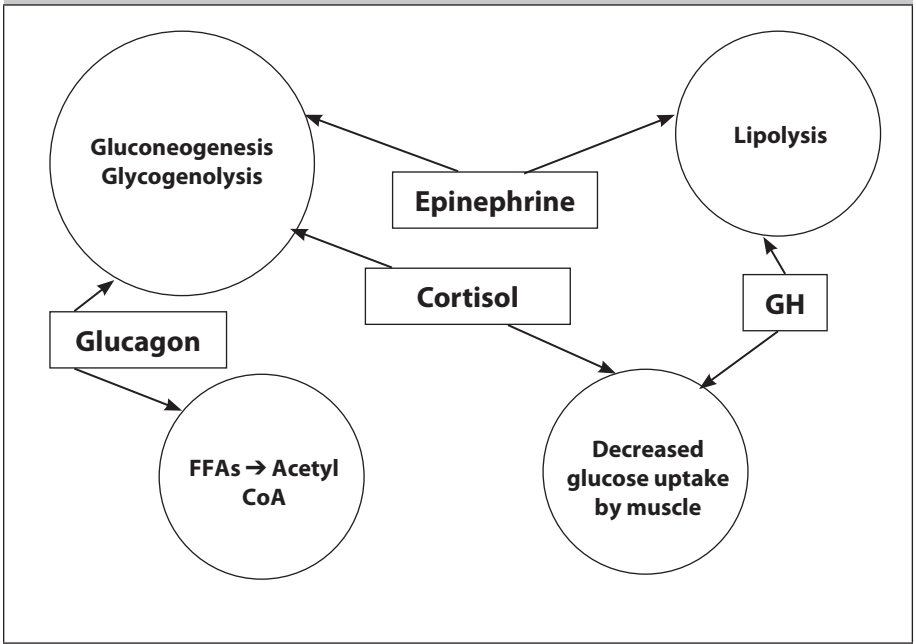


Figure 2. Counter-regulatory Hormones



While insulin is deficient, counter-regulatory hormones rise and cause effects that are opposite to insulin. The most counter-regulatory hormone is glucagon. The other counter-regulatory hormones, like epinephrine, cortisol, and growth hormone (GH), work synergestically with glucagon.

by comparing the difference (ΔAG) between the patient's anion gap and the normal anion gap to the difference (Δ HCO3-) between normal serum bicarbonate and patient's serum bicarbonate. In the presence of a pure or lone DKA, ΔAG is approximately equal to Δ HCO3-. If ΔAG is lower than Δ HCO3-, there is a greater fall in serum bicarbonate than one would expect in relation to the increase in the anion gap. This can be explained by the presence of an increase in another measured anion, leading to hyperchloremic acidosis in the presence of an anion gap metabolic acidosis of DKA. Decreased renal perfusion secondary to dehydration may lead to renal injury with induction of such hyperchloremic tubular acidosis. Thus, hyperchloremic tubular acidosis is one of the common causes of normal anion gap acidosis in the presence of DKA, because an additional fall in serum bicarbonate is due to further buffering of an acid that does not contribute to the anion gap. On the other hand, ΔAG > Δ HCO3- indicates a lesser fall in serum bicarbonate than one would expect in the presence of the rise in anion gap. This is explained by concurrent presence of metabolic alkalosis frequently induced by vomiting dehydration as well as by another process that increases the serum bicarbonate, e.g., primary hypercortisolism or hyperaldosteronism or due to compensatory metabolic alkalosis in the presence of chronic respiratory acidosis in a subject with a primary lung disorder. Finally, in a few instances, anion gap acidosis may occur secondary to accumulation of multiple measured and/or unmeasured anions, e.g., lactic acidosis due to inadequate tissue perfusion from severe dehydration or concurrent acute disorder such as septic shock or acute myocardial infarction (*see Table 1*).

Clinical Presentation

The metabolic abnormalities of DKA develop rapidly, often within 24 hours of absolute insulin deficiency. The onset of T1DM can be gradual, with progressive symptoms.[40-46] However, in clinical practice, DKA is often the initial manifestation, with a reported abrupt onset in children with T1DM; this may be attributed to lack of recognition of symptoms by children or their parents.

In adolescents and adults, DKA as an initial manifestation of T1DM, including latent autoimmune diabetes of adults (LADA), is rare.[47-52] In these subjects, hyperglycemia alone without ketosis is the frequent initial presentation and may be attributed to the patients' ability to recognize symptoms of hyperglycemia, such as polyuria, polydipsia, nocturia, and weight loss, leading them to seek prompt medical attention. Subjects with LADA are often diagnosed initially as T2DM

and are successfully managed with lifestyle intervention and oral agents for a short period. However, after the initial diagnosis, hyperglycemia usually recurs within 6-12 months and is not responsive, despite the use of a combination of oral agents, and is ameliorated only by administration of insulin.

In contrast, the onset of DKA in patients with T2DM is often preceded by symptoms and signs of poor glycemic control (e.g., polyuria, nocturia, polydipsia, weight loss) for several days or even months, unless precipitated by an acute disorder. The onset of ketonemia and acidosis is characterized by rapid occurrence of symptoms, e.g., anorexia, nausea, vomiting, abdominal pain, muscle cramps, and respiratory distress, which frequently present 24 to 48 hours prior to hospitalization. Many patients misconstrue onset of gastroenterological symptoms as an accompanying gastrointestinal disorder responsible for precipitating DKA.

Physical examination of patients with DKA shows the presence of ketotic breath, hyperventilation, tachycardia, orthostasis, abdominal pain, and occasionally hypothermia and/or impaired consciousness or even coma.[33] Change in mental status correlates more significantly with older age and increasing serum osmolality rather than the severity of acidosis. In the elderly, serum osmolality ≥ 340 mOsm/L is known to induce a markedly altered mental status, including confusion, convulsion, and coma.[53] Finally, hyperchloremic acidosis may ensue and persist during the recovery period more often and in a more profound pattern in subjects with T2DM manifesting DKA than subjects with T1DM (*see Table 2*).

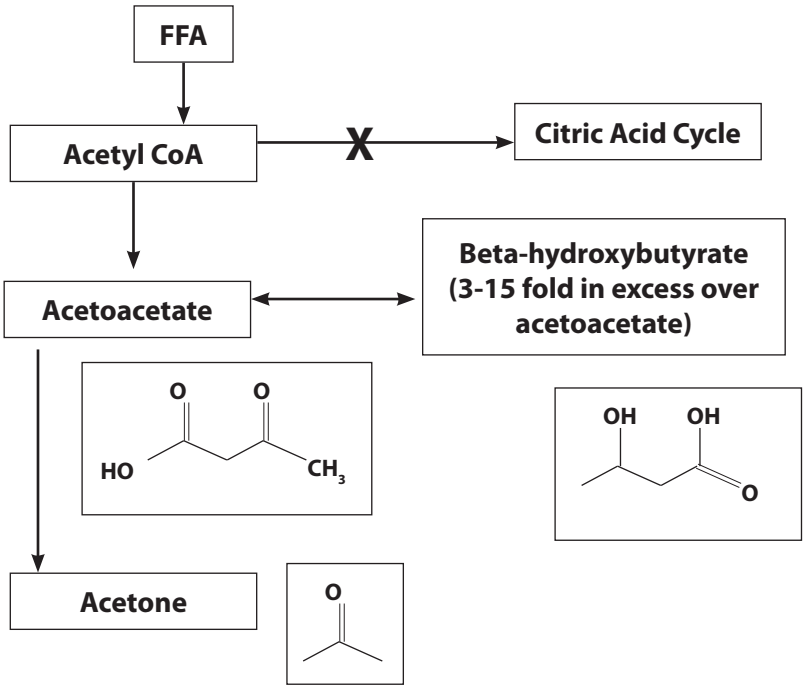
Hyperglycemia by itself does not fulfill the diagnostic criteria for DKA. High anion gap metabolic acidosis caused by elevated serum ketones, measured as beta-hydroxybutyrate, acetoacetate, or acetone, must be present in addition to hyperglycemia (≥ 250 mg/dL) to establish the diagnosis of DKA. DKA is frequently classified as mild, moderate, or severe based on the degree of acidosis and clinical manifestations (*see Table 3*).[35] Serum beta-hydroxybutyrate is present 3-5 times in excess when compared to other ketones and is the test of choice for a prompt diagnosis of DKA. Similarly, the presence of ketonemia and even ketoacidosis in the absence of hyperglycemia (≥ 250 mg/dL) does not fulfill the well-established criteria for the diagnosis of DKA. Patients partially treated with insulin prior to ED arrival may present with milder hyperglycemia but severe ketoacidosis. Ketoacidosis can also be due to alcoholic and pancreatic causes.[54-57]

Th differential diagnosis of DKA includes other forms of metabolic acidosis (*see Table 4*); specifically, ketosis and/or ketoacidosis, including:

1) DKA with laboratory findings consisting of hyperglycemia (serum glucose ≥ 250 mg/dL) and ketoacidosis (anion gap acidosis) with arterial pH ≤ 7.30 and PCO_2 ≤ 30 mmHg; and/or serum bicarbonate ≤ 18 mEq/L.

2) Alcoholic ketoacidosis manifesting with anion gap acidosis with serum glucose usually ≤ 200 mg/dL, occasionally

Figure 3. Ketone Production



DKA incites lipolysis within adipose tissue with release of free fatty acids (FFA) into the circulation, where they are beta-oxidized in the liver into acetyl-CoA. Ordinarily, acetyl-CoA would enter the Citric Acid or Krebs cycle. In DKA, many of the Citric Acid cycle intermediates (mainly oxaloacetate) have been depleted by entry into the gluconeogenesis pathway. Accumulation of acetyl-CoA leads to production of ketones and ketoacids.

Table 1. Anion Gap Acidosis and the Delta Gap

Δ AG = Δ HCO3-	Pure anion gap acidosis
Δ AG < Δ HCO3-	Anion gap acidosis + normal gap metabolic acidosis (e.g., RTA)
Δ AG > Δ HCO3-	Anion gap acidosis + metabolic alkalosis (e.g., primary aldosteronism, hypercortisolism, contraction alkalosis, and diuretic use)
Δ AG >> Δ HCO3-	Anion gap acidosis + metabolic alkalosis + primary respiratory alkalosis
Anion gap (AG) = Na = (Cl- + HCO3-)	

Table 2. DKA in T1DM and T2DM

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
65-70% of total DKA cases	30-35% of total DKA cases
pH ≤ 7.2	pH > 7.2
BMI ≤ 27 kg/m^2	BMI > 27 kg/m^2
Shorter time to achieve ketone free urine (29 h)	Longer time to achieve ketone free urine (36 h)
Infection (21.6%) as a cause of precipitant	Infection (48.4%) as a cause of precipitant

Table 3. Classification of Severity of DKA

	Mild	Moderate	Severe
Arterial pH	7.25-7.30	7.00-7.25	< 7.00
Serum bicarbonate (meq/L)	15-18	10-15	< 10
Anion gap	10-12	12-14	> 15
Mental status	Alert	Alert/drowsy	Stupor/coma

even in the hypoglycemic range often occurring after an alcohol binge followed by starvation. As in DKA, the major circulating ketone body in alcoholic ketoacidosis is also beta-hydroxybutyrate, and the serum concentration is disproportionately greater when compared with other ketones.[54,55]

3) Pancreatic ketoacidosis as a complication of severe acute pancreatitis established by anion gap acidosis with serum glucose ≤ 200 mg/dL with occasional hypoglycemia. Significant positive correlations were documented between serum lipase levels and anion gap values as well as serum pH levels (*see Table 5*).[56,57] Moreover, the decline in ketone bodies in the circulation and rise in pH follows declining serum lipase levels during recovery.

4) Starvation ketosis is characterized by the presence of ketosis rather than ketoacidosis secondary to prolonged starvation with normal serum glucose concentration.[35,36]

Management of DKA

Management of DKA involves resuscitation, IV insulin administration, and repletion of electrolytes, and simultaneous treatment of the underlying disorder precipitating DKA.

Fluid Resuscitation. Fluid loss in patients with DKA averages approximately 6-9 L in adults (*see Table 6*). The goal is to replace the total fluid loss within 24-36 hours. Fifty percent of the fluid is administered during the first 8-12 hours.[58] One accepted approach is to rapidly infuse 15-20 mL/kg (1 to 2 L) of normal saline (0.9%) over the first hour, followed by reduced infusion rate of 250 mL/hr. Once the blood glucose decreases below 250 mg/dL, IV fluid is changed to 5% dextrose/0.45% saline.[58-63]

Fluid with electrolytes may be required to be administered orally or via nasogastric tube in patients in whom obtaining an IV site proves difficult due to volume depletion. In rural sites, especially in developing countries, these routes of administration may also be preferred in the absence of availability of equipment for IV infusion. Although the composition of lactated Ringer's is closer to that of plasma when compared to normal saline, there is no benefit to lactated Ringer's over normal saline in the treatment of DKA.[61-63] In addition, the time to recovery of glucose to desirable glucose level is longer with lactated Ringer's solution when compared to normal saline.[61-63]

Insulin Administration. Insulin lowers serum glucose by promoting glucose uptake by peripheral tissues and by inhibiting glycogenolysis and gluconeogenesis. In addition to correction of serum glucose, insulin also inhibits lipolysis, including triglyceride breakdown, thus eliminating substrates such as free fatty acids for ketogenesis and, therefore, ameliorates ketoacidosis.[64,65]

Insulin is essential in the treatment of DKA, but it must be administered after initial fluid administration and serum potassium is above 3.3 mEq/L. In the absence of fluid and electrolyte replacement, insulin may lead to a shift of fluid from extracellular space back into the cells, leading to intravascular dehydration in the presence of excess body water, resulting in persistence of hypotension. Additionally, acidosis often may not resolve simultaneously with a decline in plasma glucose because the hydration itself can induce renal tubular acidosis via suppression of plasma renin activity and aldosterone.

The objectives of insulin administration include gradual lowering of plasma glucose and amelioration of ketoacidosis. Serum glucose reduction at the rate of 10% per hour from the initial concentration is recommended to avoid adverse outcomes. A greater rapid decline in blood glucose concentration increases the risk of hyperosmotic encephalopathy (cerebral edema).[24-26] Therefore, blood glucose concentration should be monitored hourly at the bedside with a point-of-care glucose meter.

The IV route is considered to be the most optimal because it promotes direct entry of insulin into circulation and is, therefore, the most accepted and established approach of insulin administration.[64-75] This route is absolutely essential in the presence of hypotension due to severe dehydration occurring in many subjects with DKA. Absorption of insulin and its entry into circulation is hampered with any other route of administration (e.g., subcutaneous or intramuscular) and therefore is distinctly suboptimal. Moreover, IV administration is also convenient because of the ease of adjustment of the infusion rate as well as repeated administration of the bolus dose if required to obtain desirable lowering of glycemia. All types of insulin attain a similar serum profile when administered intravenously.[66,76]

Table 4. Differential Diagnosis of High Anion Gap Metabolic Acidosis

High Anion Gap Metabolic Acidosis	Normal Anion Gap Metabolic Acidosis
Common	**Low Potassium**
• Lactic acidosis • Ketoacidosis • Acute kidney injury • Chronic kidney disease • Methanol poisoning • Ethylene glycol poisoning • Salicylate poisoining	• Renal tubular acidosis • Carbonic anhydrase inhibitors • Ureteral diversions • Diarrhea • Surgical drainage or fistula • Posthypocapneic acidosi
Uncommon	**Normal/High Potassium**
• Diethylene glycol poisoning • Propylene glycol poisoning • 5-oxoproline acidosis • d-lactic acidosis	• Renal tubular acidosis • Early renal failure • Hydronephrosis • Low aldosterone • Drug induced • Addition of inorganic acid • Sulfur toxicity • Cholestyramine
	Other
	• Expansion acidosis • Cation exchange resin

Table 5. Laboratory Findings in Acute Pancreatitis

Serum lipase concentrations as well as anion gap [Sodium –(chloride + bicarbonate)] and arterial pH values in 18 subjects with acute pancreatitis divided into three groups: K_0 with neither ketonuria nor ketonemia, K_1 with ketonuria alone without ketonemia, and K_2 with both ketonuria and ketonemia.

Group	No. of Subjects	Serum lipase U/L	Anion Gap nm/L	Arterial pH
Neither ketonuria or ketonemia	5	304 ± 22	11.6 ± 1.3	7.42 ± 0.03
Ketonuria but not ketonemia	6	438 ± 64*	17.7 ± 1.4*	7.33 ± 0.03*
Both ketonuria and ketonemia	7	779 ± 110‡≠	27.6 ± 2‡≠	7.27 ± 0.02‡≠
		(23-190)$	(12-15)$	(7.35-7.45)$

* $P < 0.01$ vs K_0
‡ $P < 0.001$ vs K_0
≠ $P < 0.01$ vs K_1
$ Normal range in parenthesis

Table 6. Fluid and Major Electrolyte Losses in DKA

Water	100 mL/kg (60-110)
Sodium	6 mEq/kg (5-13)
Potassium	5 mEq/kg (4-6)

The aim of IV bolus administration is to raise the serum insulin level promptly, which is then maintained at a steady state by continuous IV infusion. Administration of insulin infusion alone delays the rise in serum insulin concentration required for prompt desirable lowering of glucose and amelioration of ketoacidosis. The initial insulin dose is based on the patient's body weight (0.1 unit/kg). IV bolus administration is followed by a continuous insulin infusion at a rate of 0.1 unit/kg/hr. IV bolus followed by infusion is the standard with which alternative insulin strategies are compared.[71,72] However, some studies have questioned the benefit of the initial bolus compared to administration of the continuous infusion alone.[70-71] A study by Kitabchi et al examined the comparative efficacy of an insulin priming dose followed by continuous insulin infusion at two different hourly rates with continuous infusion without a priming dose.[73] Patients were divided into three groups: 1) load group of 12 patients using a priming IV dose of 0.07 units of regular insulin per kg body weight followed by a continuous IV infusion with a dose of 0.07 units/kg/hr; 2) no load group of 12 patients using an IV infusion of regular insulin of 0.07 units/kg/h without a priming IV dose; and 3) twice no load group of 13 patients using an IV infusion of regular insulin of 0.14 units/kg/h (i.e., twice the dose in group 2) without a priming dose. The study concluded that the times to reach glucose < 250 mg/dL were not significantly different among the groups. However, several patients in the group not administered the priming or the bolus insulin dose required "supplemental" insulin to decrease the initial glucose levels by 10%.[71] Another study suggested that lower insulin dose (0.5-4 units/hour) may be as effective as the currently recommended dose of 0.1 unit/kg/hour. However, the duration of therapy required to achieve desirable glycemia and remission of ketoacidosis was longer at these lower insulin infusion rates.[74]

Moreover, in all of these studies,[72-74] the blood glucose levels of patients at diagnosis of DKA were only mild-to-moderately high (< 500 mg/dL) and the number of subjects in these studies was relatively small to draw appropriate and definitive conclusions. A retrospective study by Bradley and Tobias reviewed

the therapy of DKA in children admitted to the pediatric intensive care unit over a 10-year period.[75] This retrospective study compared two protocols: 1) administration of IV bolus of insulin 0.24 ± 0.27 units/kg body weight followed by continuous infusion; and 2) continuous insulin infusion alone. Patients who received continuous infusion alone required longer duration of therapy for achieving the desirable glycemic goal as well as resolution of DKA.[7]

Based on this evidence, it is prudent to implement the insulin therapy based on the severity of hyperglcyemia and/or ketoacidosis. For example, in a patient presenting with initial blood glucose of 800 mg/dL, administration of continuous IV infusion without the bolus may delay appropriate lowering of blood glucose control due to required duration of treatment. On the other hand, in a patient presenting with blood glucose of 300 mg/dL, IV bolus prior to continuous insulin therapy may not be necessary.

The rate of insulin infusion should be reduced if the decline in blood glucose is > 10% per hour and can be adjusted based on the following formula: Units of regular insulin/h = (glucose - 60) × 0.01 or 0.02. American Diabetes Association (ADA) guidelines for management of DKA recommend gradual reduction in the rate of IV insulin infusion and initiation of subcutaneous insulin administration in a multiple daily-dose schedule when the blood glucose declines to ≤ 200 mg/dL and two of the following goals are attained: serum anion gap < 12 mEq/L (or at the upper limit of normal range for the local laboratory), serum bicarbonate ≥ 15 mEq/L, arterial blood pH > 7.30, and resumption of oral intake.[1]

Maintenance insulin therapy in diabetes mellitus uses basal plus prandial dosing to replicate normal physiologic insulin secretion.[77] Basal insulin controls hyperglycemia between meals and during overnight fast, whereas rapid-acting insulin helps attain desirable postprandial glycemic excursions. The currently approved basal insulin formulations include the newer insulin analogs — insulin glargine and insulin detemir — as well as older intermediate-acting neutral protamine hagedorn (NPH) insulin.[77-80] It is important to overlap the IV insulin infusion and the subcutaneous insulin for 1-2 hours prior to stopping the IV insulin. Abrupt discontinuation of insulin infusion acutely reduces serum insulin levels and may result in recurrence of hyperglycemia and/or ketosis.[64-75,82-85]

Patients with established diagnosis of T1DM prior to onset of DKA may be reinitiated on their home subcutaneous insulin regimen on resumption of oral caloric intake.[1] In insulin-naive patients with T1DM, a multiple daily dose subcutaneous insulin injection regimen should be started at a dose of 0.5-0.6 units/kg per day, including bolus and basal insulin, until an optimal dose is established. The usual distribution of daily insulin dose is 50% basal and 50% prandial. Prandial daily dose usually is divided into three mealtime dosages. For example, a 72 kg male may require a total of 36 units — half of this dose (18 units) would be the basal dose and the other half (18 units) may be divided into three dosages of six units administered with each meal. Another alternative is to administer mealtime insulin dosage based on the amount of carbohydrate intake by educating patients about carbohydrate counting.

Treatment with a basal-prandial regimen is proactive and prevents hyperglycemia, whereas a sliding scale regular insulin regimen administered alone subcutaneously at an interval of 6 hours is suboptimal and, hence, is not recommended.[83-85] Subjects with T2DM may be discharged on the same regimen as the inpatient insulin regimen but need to be followed up promptly within 1-2 weeks to assess the need for continuing insulin therapy or reversing to their prior hypoglycemic therapy, including lifestyle modification, oral hypoglycemic agents, and/or insulin therapy.

Electrolytes

Two major depleted electrolytes in DKA include sodium and potassium (*see Table 6*). However, losses also involve other electrolytes, such as chloride, phosphate, and magnesium. Osmotic diuresis secondary to hyperglycemia is the major contributing factor to total body losses of almost all electrolytes including sodium.

Serum sodium may vary from subnormal to supernormal concentrations due to depletion as well as a shift from extracellular compartment to intracellular milieu due to hyperosmolarity. Serum sodium should be "corrected" in the presence of hyperglycemia. There is debate about the appropriate correction factor to use. Most commonly, this formula is used: Corrected Serum Sodium = Measured Serum Sodium + 0.016 × (Serum Glucose (mg/dL) - 100).

Total body potassium is depleted in DKA due to osmotic diuresis. However, serum potassium levels may be variable at the time of patient presentation. High serum potassium levels are attributed to a shift of potassium from intracellular space to extracellular space due to acidosis and lack of insulin. Normal or low serum potassium may be present despite acidosis and extracellular shift due to extreme depletion of total body potassium secondary to hyperglycemic osmotic diuresis. Administration of insulin and IV fluid facilitates intracellular influx of potassium, magnesium, and phosphate and may lead to a decline in serum concentrations of these electrolytes.[37-39,86] Additionally, hydration with normal saline improves renal blood flow, facilitating tubular exchange of potassium for sodium, promoting urinary excretion of potassium, chloride, phosphate, and magnesium.[37-39,89] Therefore, frequent and close monitoring of potassium, phosphate, and magnesium is crucial.

Maintaining normal serum potassium is critical as low levels may lead to cardiac arrhythmias and death. The average potassium deficit in DKA is 3-5 mEq/kg body weight, although it may be as high as 10 mEq/kg body weight in some subjects. Potassium must be replaced once the serum level starts declining below 5 mEq/L, with the goal of maintaining the serum potassium level between 4-5 mEq/L.[1] IV administration is preferred for potassium repletion at a rate of 10 mEq/hr. However, in circumstances involving lack of venous access due to dehydration or lack of equipment in developing or least developed countries, oral or enteral potassium supplementation may be used. In patients with nausea and inability to

Table 7. Common Precipitants of DKA

Inadequate insulin treatment or noncompliance
New onset diabetes (20-25%)
Acute illness: • Infection (30-40%) • Cerebral vascular accident • Myocardial infarction • Acute pancreatitis
Drugs: • Clozapine or olanzapine • Cocaine • Lithium • Terbutaline

Table 8. Complications in DKA

Complications Due to DKA	Complications Due to Treatment of DKA
• Vascular occlusion-MI, CVA, mesenteric, others • Acute renal failure • Pancreatitis • Erosive gastritis • Acute gastric distention	• Cerebral edema • ARDS • Hypokalemia • Fluid overload • Line infection/thrombosis • Relapse of DKA on transfer to floor • Hypoglycemia • Hyperchloremic acidosis

ingest potassium tablets, a nasogastric tube may be inserted for administration via this route.

Bicarbonate therapy for correcting acidosis in DKA has not been shown to improve patient outcomes and may actually induce potentially serious complications, such as hypokalemia, rebound metabolic alkalosis, and delay in improvement of both hyperosmolarity and ketosis.[87-89] Furthermore, in DKA patients with an initial pH < 7.0, IV bicarbonate therapy does not decrease the time to resolution of acidosis or shorten the period of hospital stay. Bicarbonate administration also has been implicated as a risk factor for cerebral edema in children.[90]

In adults, cerebral acidosis may lag behind serum acidosis with bicarbonate therapy and may cause disequilibrium between cerebral pH and serum pH, leading to worsening or persistence of altered mental status.[90,91] Finally, because of the potential adverse cardiovascular outcomes, the ADA guidelines recommend using bicarbonate only when the serum pH is < 6.9 with a prompt correction to 7.0-7.1 and/or with simultaneous presence of lactic acidosis.[1]

Once the treatment of DKA is initiated, it is important to identify an underlying acute disorder frequently responsible for induction of DKA (*see Table 7*) and institute appropriate management. Adverse outcomes due to DKA and during administration of fluids, insulin, and electrolytes should be anticipated (*see Table 8*). Dehydration may lead to vascular events such as myocardial infarction, stroke, mesenteric thrombosis, and peripheral vascular occlusion secondary to rise in serum viscosity. Cerebral edema is a rare adverse outcome occurring during the treatment of DKA in patients and is attributed to rapid glucose lowering, especially in patients at extremes of age. Treatment of DKA may result in complications such as hypoglycemia, hypokalemia, hyperchloremic acidosis, cerebral edema, acute respiratory distress syndrome, and fluid overload with generalized edema.[91]

Prevention

Prevention of DKA consists of key management principles. Diabetic educators and other providers should educate patients and their caregivers on daily diabetic management as well as during special occasions such as traveling.

Education of patients and/or their caregivers should include blood glucose goals as well as frequency of administration of rapid-acting insulin to achieve recommended glycemic goals. Finally, it is equally important to educate patients and their next of kin or caregivers that rapid-acting insulin should not be withheld during illness, even if patients lose their appetite and are unable to eat. In this situation, blood sugar should be monitored with subcutaneous insulin based on those values. Self-monitoring of blood glucose at frequent intervals is the most important maneuver, since persistent hyperglycemia is the precursor to progression to hyperglycemic crisis including DKA. Recommended blood sugar goals are preprandial capillary plasma glucose reading of 80-130 mg/dL and peak postprandial capillary plasma glucose level of < 180 mg/dL.[92-95]

Patients using an insulin pump may need to discontinue the pump during illness and administer rapid-acting subcutaneous insulin at 4-6 hours, since use of the pump is shown to be inadequate in attaining and maintaining desirable blood sugars. Therefore, all patients using insulin pumps should be educated about backup protocols for administering basal and rapid-acting insulin as well as the supplies needed to implement the protocol during illness.

Clinical indicators for seeking medical care include > 5% loss of body weight, respiration rate > 36/min, persistently elevated blood glucose, mental status change, uncontrolled fever, unresolved nausea, and vomiting.[1] Patients should be instructed and encouraged to seek early medical care in order to prevent progression of illness, hyperglycemia, and critical complications (e.g., DKA and other hyperglycemic emergencies).

Conclusion

DKA is a potentially life-threatening disorder in patients with both T1DM and T2DM. Prompt recognition of the disorder and appropriate laboratory testing, followed by efficient management with appropriate fluid resuscitation, electrolyte replacement, and adequate insulin therapy, is crucial for preventing adverse outcomes including death. DKA management requires recognizing the laboratory turnaround time and the practical aspects of administration of fluid, electrolytes, and insulin. Prevention of recurrence must be a

major goal in every patient hospitalized for DKA. This can be achieved by educating both patients and caregivers and by providing appropriate management protocols for implementation during travel and sick days. With appropriate management, mortality in adult patients with DKA is almost negligible.

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CME/CE Questions

1. Which of the following is *not true* regarding DKA?
   A. About 30-35% of cases are see in Type 2 diabetes mellitus.
   B. DKA with mild-to-moderate hyperglycemia has been reported after initiation of SGLT2 inhibitors.
   C. Continuous subcutaneous insulin infusion pumps using rapid-acting insulin also have been associated with a significant decrease in the incidence of DKA compared to conventional therapy.
   D. Mortality due to complications of DKA is rare in both adults and children.
2. Which of the following is *not* a counter-regulatory hormone to insulin?
   A. Prolactin
   B. Glucagon
   C. Cortisol
   D. Growth hormone
3. What is the most commonly reported precipitant of DKA in Type 2 diabetes mellitus?
   A. Stroke
   B. Infection
   C. Myocardial infarction
   D. Trauma
4. Fluid loss in adult patients with DKA is approximately:
   A. 1-2 L.
   B. 3-4 L.
   C. 6-9 L.
   D. 10-12 L.
5. When should IV insulin therapy be started in DKA?
   A. Immediately on diagnosis
   B. After fluid deficit has been completely restored
   C. After acidosis has been treated and arterial or venous pH is > 7.25
   D. After initial fluid bolus and serum potassium is > 3.3 mEq/L
6. What is true about the use of intravenous sodium bicarbonate in DKA?
   A. It should be used only if arterial or venous pH < 6.9.
   B. It should not be used in simultaneous presence of lactic acidosis.
   C. Its use shortens the duration of acidosis.
   D. Its use reduces the incidence of cerebral edema in children with DKA.

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