

Title Diabetic Ketoacidosis versus Hyperosmolar Hyperglycemia State
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Contact Hour 1

Purpose

The goal of this course is to describe Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS). Then to learn to recognize the difference between DKA and HHS, the pathogenesis, treatments and complication of DKA and HHS.

Objectives

1. To describe the presentation of DKA and HHS.
 2. To understand the pathogenesis of DKA and HHS and why they are different.
 3. To be aware of the different algorithmic treatment protocols for DKA and HHS.
 4. List the complications of DKA and HHS.
 5. To understand the prevalence of Diabetes in the United States.
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Diabetic ketoacidosis (DKA) and the Hyperglycemic hyperosmolar state (HHS) are the most serious complications of diabetic decompensation and remain associated with excess mortality. (1). Insulin deficiency is the main underlying abnormality. Insulin deficiency can trigger hepatic glucose production and reduced glucose uptake, resulting in hyperglycemia, and can also stimulate lipolysis and ketogenesis, resulting in ketoacidosis. Both hyperglycemia and hyperketonemia will induce osmotic diuresis, which leads to dehydration.

Incidence

In 2002, an estimated 6.3% of the population (about 18.2 million people) had diabetes. (7). Type 2 diabetes mellitus accounts for 90% to 95% of cases, and people 65 years or older make up almost 40 % of all persons with diabetes. The prevalence of type 2 diabetes mellitus is increasing dramatically and parallels the epidemic of obesity.

Mortality rates are 2-5% for DKA and 15% for HHS, and mortality is usually a consequence of the underlying precipitating causes rather than a result of the metabolic changes of hyperglycemia. (10). Effective standardized treatment protocols, as well as prompt identification and treatment of the precipitating cause, are important factors affecting outcome.

DKA still remains a significant cause of hospital admissions. (3). DKA tends to occur in individuals younger than 19 years, but it may occur in patients with diabetes at any age. (8). DKA occurring at the time of diagnosis of diabetes is more common in younger children. (12). It may be the first indication that a patient has developed diabetes. Treating DKA can be costly and may require a stay in an acute care environment. It has been estimated that the annual cost of treating DKA may be at least \$1 billion in the United States.

HHS carries a higher mortality rate than DKA. (7). In 30-40% of cases it is the initial presentation of a patient with diabetes. It is associated with a serious concurrent illness. It is

usually seen in older patients, but may present at any age. HHS is less common than DKA. The mean age of patients is 60 years, yet cases in pediatric patients are reported.

Pathogenesis

DKA is characterized by hyperglycemia, metabolic acidosis, and increased circulating total body ketone concentration. (10). Ketoacidosis results from the lack of, or ineffectiveness of, insulin with concomitant elevation of counterregulatory hormones (glucagons, catecholamines, cortisol, and growth hormone). The association of insulin deficiency and increased counterregulatory hormones leads to altered glucose production and disposal, increased lipolysis and production of ketone bodies. Hyperglycemia results from increased hepatic and renal glucose production (gluconeogenesis and glycogenolysis) and impaired glucose utilization in peripheral tissues. Hyperglycemia and high ketone levels cause osmotic diuresis that leads to hypo-volemia and decreased glomerular filtration rate. Glucose is osmotically active and creates an osmotic gradient drawing water from the intracellular to extracellular compartments.(7). This further aggravates hyperglycemia.

Persons presenting with DKA are often seriously ill, not only because DKA itself is a metabolic catastrophe, but also because significant underlying infection or other disorders might be present. (4).

Classic symptoms of hyperglycemia (8). (5).

- thirst
- polyuria, polydipsia
- nocturia

Other symptoms

- generalized weakness
- malaise/lethargy
- nausea/vomiting
- decreased perspiration
- fatigue
- anorexia or increased appetite
- confusion

Symptoms of associated infections and conditions

- fever
- dysuria
- chills
- chest pain
- abdominal pain
- shortness of breath

General signs

- Ill appearance
- dry skin
- labored respirations
- dry mucous membranes
- decreased skin turgor

- decreased reflexes

Vital Signs

- tachycardia
- hypotension
- tachypnea
- hypothermia
- fever, if infection

Specific signs

- ketotic breath (fruity, with acetone smell)
- confusion
- coma
- abdominal tenderness

The most common scenarios are underlying or concurrent infection (40%), missed insulin doses (25%), and newly diagnosed previously unknown diabetes (15%). Other associated causes make up about 20%.

Urinary tract infections are the single most common infection associated with DKA, but many other associated illnesses need to be considered.

The clinical presentation of DKA usually develops rapidly, over a period of < 24 hours. (10). Polyuria, polydipsia, and weight loss may be present for several days before the development of ketoacidosis. Vomiting and abdominal pain are frequently the presenting symptoms. Abdominal pain, sometimes mimicking an acute abdomen, is reported in 40-75% of cases of DKA. Acetone on breath and labored Kussmaul respiration may also be present on admission, particularly in patients with severe metabolic acidosis.

The key pathophysiological event in HHS is relative or absolute deficiency of insulin activity. (9). Deficient insulin activity may arise from an increase in insulin resistance or an inadequate supply of insulin, either endogenously or exogenously.

In a diabetic patient with pre-existing insulin lack or resistance, a physiologic stress, like an acute illness, can cause further net reduction in the effectiveness of circulating insulin.(7). Concomitant elevations in counter regulatory hormones, glucagons, catecholamines, cortisol, and growth hormone, contribute to impaired glucose use in the peripheral tissues. As in DKA, the combination of hepatic glucose production and decreased peripheral glucose use is the main pathogenic etiology for HHS.

Hyperglycemia leads to glycosuria, hypotonic osmotic diuresis, and dehydration. Glucose is osmotically active and creates an osmotic gradient drawing water from the intracellular to extracellular compartments. If fluid intake is adequate, renal excretion of glucose may be sufficient to prevent marked serum hyperglycemia. It is this renal insufficiency in HHS that allows for the extremely high levels of glucose seen with this disorder, much higher than DKA, resulting in the severe hyperosmolality and intracellular dehydration.

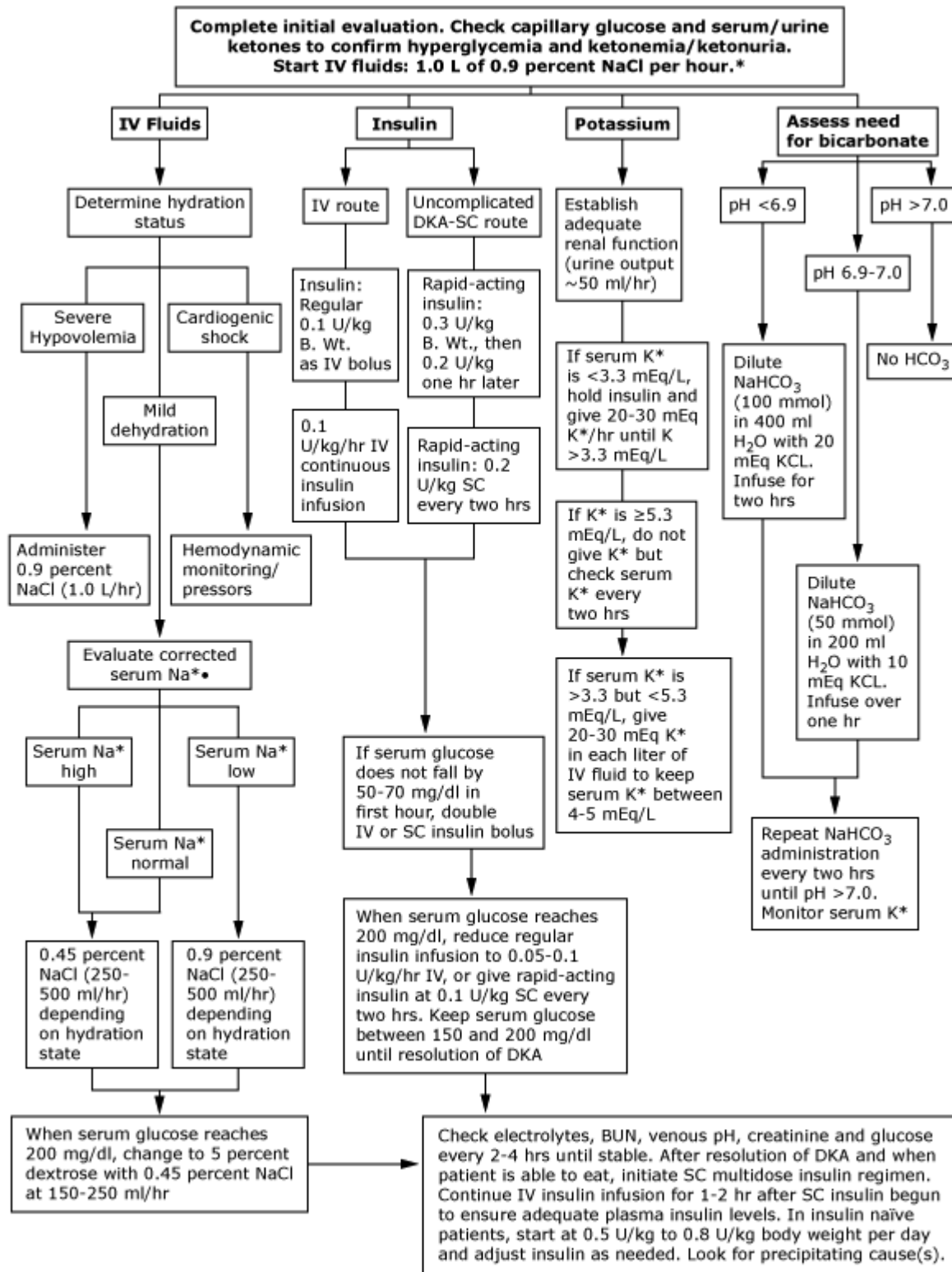
The full development of HHS occurs over several days, and the total body water deficit averages 8 to 12 liters in HHS, compared with 5 to 7 liters in DKA. In its severe form, this prolonged osmotic diuresis results in hypotension and impaired tissue perfusion. (7)

Treatment

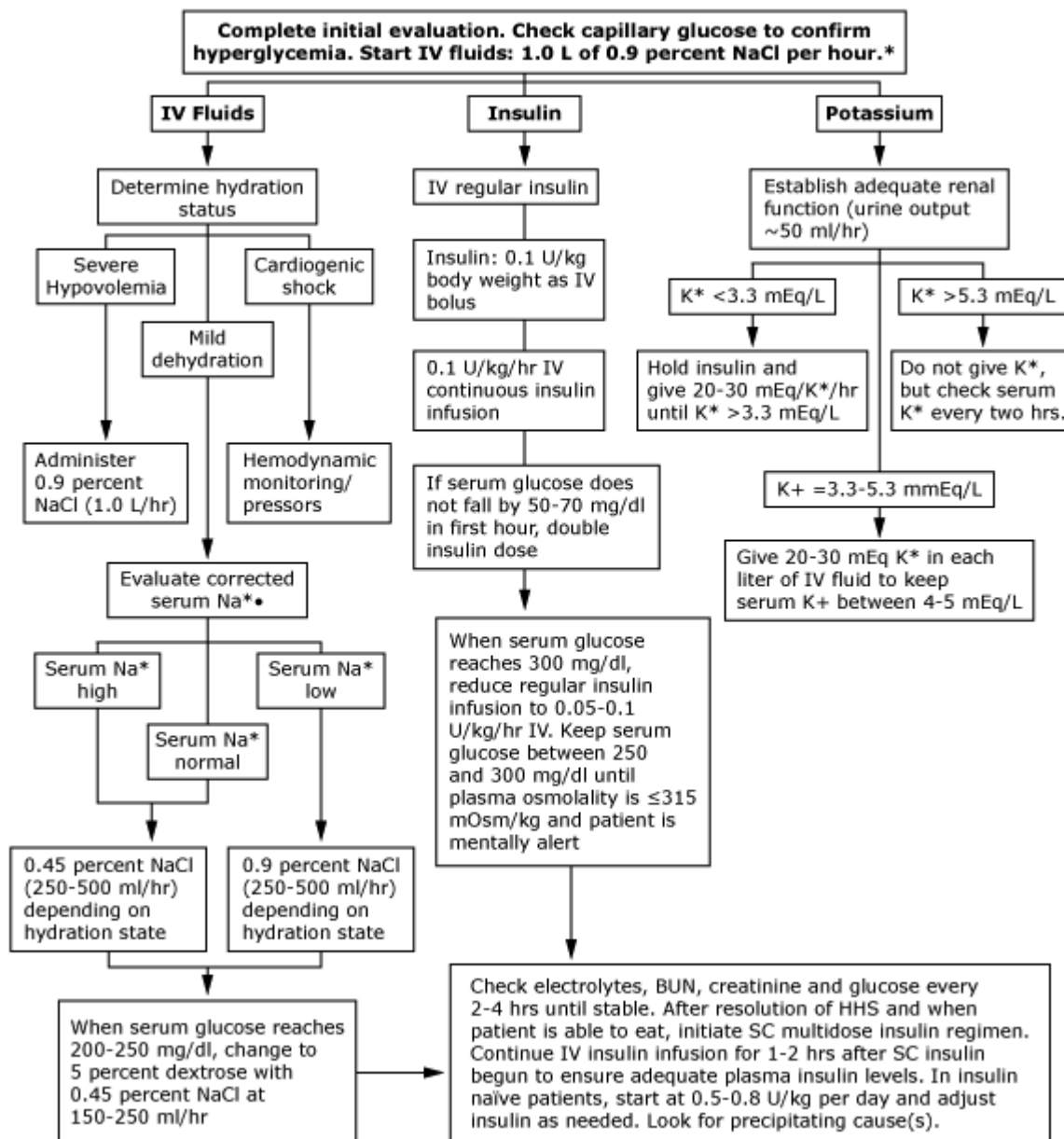
The main objective in the treatment of DKA and HHS is to correct water and electrolyte imbalance over the first 24- 48 hours, to refill extracellular fluid volume and restore intravascular volume. (2). Depending on the hospital facilities, patients are generally admitted to either intensive-or intermediate-care areas where nursing ratios allow for the necessary monitoring. (3).

An algorithmic approach is shown in the flow diagrams for treating DKA (algorithm 1) and HHS (algorithm 2).

Protocol for the management of adult patients with DKA.(6)



Protocol for the management of adult patients with HHS. (6).



Initial Evaluation

Both DKA and HHS are medical emergencies that require prompt recognition and management. (6). An initial history and rapid but careful examination should focus on:

- Airway, breathing, and circulation
- Mental status
- Possible precipitating events (infection, MI)
- Volume status

The initial laboratory evaluation of a patient with suspected DKA or HHS should include determination of:

- Serum Glucose

- Serum electrolytes (with calculation of anion gap), BUN and Creatinine
- Complete blood count with differential
- Urinalysis, and urine ketones by dipstick
- Plasma osmolality
- Serum ketones (if urine ketones are present)
- Arterial blood gases if serum bicarbonate is substantially reduced
- Electrocardiogram

Additional testing, such as cultures of urine, sputum, and blood, serum lipase and amylase, and chest x-ray, should be performed on a case by case basis.

The success of treatment of DKA and HHS depends on adequate correction of dehydration, hyperglycemia, ketoacidosis, and electrolyte deficits. (1).

Monitoring

The serum glucose should initially be measured every hour until stable, while serum electrolytes, BUN, creatinine, osmolality, and venous pH (for DKA) should be measured every two to four hours, depending upon disease severity and clinical response. (6).

Repeat arterial blood gases are unnecessary during the treatment of DKA; venous pH, which is about 0.03 units lower than arterial pH, is adequate to assess the response to therapy and avoids the pain and potential complications associated with repeated arterial punctures.

Anion gap metabolic acidosis (5).

The severity of metabolic acidosis is dependent upon a number of factors:

- The rate of ketoacid production
- The duration of increased ketoacid production. The acidosis will be less severe in patients who present early due, as an example, abdominal pain or underlying infection that precipitated the ketoacidosis.
- The rate of acid excretion in the urine. Patients with relatively normal renal function can markedly increase acid excretion, thereby minimizing the severity of the acidosis.

The serum anion gap provides an estimate of the quality of unmeasured anions in the serum, such as albumin and in DKA, ketoacid. It is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium):

Serum anion gap = Serum sodium - (serum chloride + bicarbonate)

Patients with DKA most often present with a serum anion gap greater than 20 meq/liter.

The increase in anion gap is variable, being determined by two factors: the rate and duration of ketoacid production; and the rate of loss of ketoacid anions in the urine.

The rate of ketoacid anions excreted depends upon the degree to which glomerular filtration is maintained. As previously stated, patients with relatively normal renal function can lose large quantities of ketoacids load, which decreases the elevation in anion gap. Rarely, patients excrete so much ketoacids that they present with only a small elevation in serum anion gap.

Fluid replacement

Initial fluid replacement is directed toward expansion of the intravascular volume and restoration of renal perfusion. (6). Adequate rehydration with subsequent correction of the hyperosmolar state results in a more robust response to low dose insulin therapy.

The average fluid loss is 3-6 liters in DKA and up to 8-10 liters in HHS, due largely to the glucose osmotic diuresis. In addition to inducing water loss, glucosuria results in the loss of approximately 70 meq of sodium and potassium for each liter of fluid lost. The aim of therapy is to replete the extracellular fluid volume without inducing cerebral edema due to rapid reduction in the plasma osmolality.

Fluid replacement is usually initiated with isotonic saline (0.9 percent sodium chloride). This solution will replace the fluid deficit, correct the extracellular volume depletion more rapidly, lower the plasma osmolality, and reduce the serum glucose concentration both by dilution and by increasing urinary losses as renal perfusion is increased.

The optimal rate at which isotonic saline is given is dependent upon the clinical state of the patient. Isotonic saline should be infused as quickly in patients who are in shock. In the absence of cardiac compromise, isotonic saline is infused at a rate of 15 to 20 ml/kg body weight per hour the first few hours.

Most patients are switched to one-half isotonic saline to replace the free water loss induced by the osmotic diuresis. When this should occur is uncertain, because of concern about the possible development of cerebral edema.

Successful progress with fluid replacement is judged by frequent hemodynamic and laboratory monitoring. Fluid replacement should correct estimated deficits within the first 24 hours. In patients with renal or cardiac compromise, more frequent monitoring must be performed during fluid resuscitation to avoid iatrogenic fluid overload.

Effect of potassium supplementation

The timing of one-half isotonic saline therapy may be influenced by potassium balance. Almost all patients with DKA or HHS have a substantial potassium deficit due to urinary, and in some cases gastrointestinal, losses. However, because of a shift of potassium out of the cells, the serum potassium is often elevated at presentation. In such patients, potassium repletion is not begun until the serum potassium concentration falls below 5.3 meq/liter.

Potassium repletion affects the saline solution that is given since potassium is as osmotically active as sodium. If 40 meq of potassium is added to each liter, one-half isotonic saline should be used if the patient is hemodynamically stable since this solution contains 117 meq of cation (77meq of sodium and 40 meq of potassium) and is therefore equivalent to approximately three-quarters isotonic saline. In contrast, the addition of potassium to isotonic saline results in the generation of a hypertonic fluid that will not correct the hyperosmolality.

Insulin

The serum glucose concentration frequently exceeds 1000mg/dL in HHS, but is generally below 800 mg/dL in DKA. (5).

Insulin therapy lowers the serum glucose concentration, diminishes ketone production and may augment ketone utilization. Any dose of insulin that corrects the hyperglycemia will also normalize ketone metabolism. (6). The only indication for delaying insulin therapy is a serum potassium below 3.3 meq/L, since insulin will worsen the hypokalemia by driving potassium into

the cells.

Regular insulin by continuous intravenous infusion is the treatment of choice, unless the episode of DKA is uncomplicated and mild. Therapy is begun with an intravenous bolus of regular insulin at 0.1 U/kg per hour. The insulin dose is the same in DKA and HHS.

This low dose of insulin usually decreases the serum glucose concentration by 50 to 70mg/dl per hour or more. If the serum glucose does not fall by 50 to 70mg/dL from the initial value in the first hour, the bolus should be repeated and the insulin infusion may be doubled every hour until a steady glucose decline is achieved. When glucose levels fail to fall with therapy, the intravenous access should be checked to make certain that the insulin is being delivered.

When the serum glucose reaches 200mg/dl in DKA or 250 to 300mg/dL in HHS, the intravenous saline solution is switched to dextrose in saline, and it may be possible to decrease the insulin infusion rate to 0.05 to 0.1 U/kg per hour. Reducing the serum glucose at this time below 200mg/dl in DKA or 250 to 300mg/dL in HSS may promote the development of cerebral edema.

Complications

The most common complications of DKA and HHS, hypoglycemia and hypokalemia, have been reduced significantly since the administration of low dose insulin. (6).

Cerebral edema in uncontrolled diabetes mellitus occurs within 12 to 24 hours of the initiation of treatment. Headache is the earliest clinical manifestation, followed by lethargy, and decreased arousal. Neurological deterioration may be rapid, with seizures, incontinence, papillary changes, bradycardia, and respiratory arrest.

The following preventive measures may reduce the risk of cerebral edema in high-risk patients.

- Gradual replacement of sodium and water deficits in patients who are hyperosmolar, with the maximum reduction in plasma osmolality being 3 mosmol/kg per hour.

The addition of dextrose to the saline solution once the serum glucose levels reach 200mg/dL in DKA or 250 to 300mg/dl until the hyperosmolality and mental status changes improve and the patient is clinically stable.

Noncardiogenic pulmonary edema

Hypoxemia and rarely noncardiogenic pulmonary edema can complicate the treatment of DKA. Hypoxemia is attributed to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance. Patients with DKA who have a widened alveolar-arterial oxygen gradient noted on initial blood gas measurement or rales on physical examination appear to be at higher risk for the development of pulmonary edema.

DKA or HHS resolution

The hyperglycemic crisis is considered to be resolved when the following goals are reached:

1. The ketoacidosis has resolved, as evidenced by normalization of the serum anion gap. As mentioned above, ketonemia and ketonuria may persist for more than 36 hours due to the slower removal of acetone.
2. Patients with HSS are mentally alert and plasma osmolality is below 315 mosmol/kg.

3. The patient is able to eat.

ADA guidelines and some authors suggest that the intravenous insulin infusion can be tapered, and a multiple-dose subcutaneous insulin schedule started, in patients who meet the following goals:

- Serum glucose below 200mg/dL in DKA or 250 to 300 mg/dL in HHS
- Serum anion gap <12 meq/L
- Serum bicarbonate >18 meq/L
- Venous pH>7.30

Prevention

The financial burden of DKA and HHS is estimated to exceed \$1 billion per year. The most common precipitating causes of DKA and HHS include infection, intercurrent illness, psychological stress, and noncompliance with therapy. Many episodes could be prevented through better and novel approaches to patient education and effective outpatient treatment programs.

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Course Exam

1. HHS is characterized by hyperglycemia, metabolic acidosis, and increased circulating total body ketones concentration.
 True False
2. Insulin deficiency is the main underlying abnormality of DKA and HHS.
 True False
3. DKA tends to occur in individuals younger than 19 years, but it may occur in patients with diabetes at any age.
 True False
4. The clinical presentation of DKA usually develops over several days and the total body water deficit averages 8-12 liters.
 True False
5. The main objective in the treatment of DKA and HHS is to correct water and electrolyte imbalance over the first 24-48 hours.
 True False
6. Cerebral edema is the most common complication of DKA and HHS.
 True False
7. Hypoglycemia and hypokalemia, complications of DKA and HHS, have been reduced significantly since the administration of low dose insulin.
 True False
8. NPH insulin is the insulin used to correct hyperglycemia in DKA and HHS.
 True False
9. Almost all patients with DKA and HHS have a substantial potassium deficit.
 True False
10. Initial labs drawn in DKA and HHS include serum glucose, serum electrolytes, cbc, urinalysis with dip, serum ketones, abg's and plasma osmolality.
 True False