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Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment

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INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS, also known as hyperosmotic hyperglycemic nonketotic state [HHNK]) are two of the most serious acute complications of diabetes. They are part of the spectrum of hyperglycemia, and each represents an extreme in the spectrum. In addition, ketoacidosis with mild hyperglycemia or even normal blood glucose has become more common with the increased use of sodium-glucose cotransporter 2 [SGLT2] inhibitors.

The treatment of DKA and HHS in adults will be reviewed here. The epidemiology, pathogenesis, clinical features, evaluation, and diagnosis of these disorders are discussed separately. DKA in children is also reviewed separately.

- (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis".)
- (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis".)
- (See "Diabetic ketoacidosis in children: Clinical features and diagnosis".)
- (See "Diabetic ketoacidosis in children: Treatment and complications".)

DEFINITIONS

DKA and HHS differ clinically according to the presence of ketoacidosis and, usually, the degree of hyperglycemia [1-3]. The definitions proposed by the American Diabetes Association (ADA) for DKA and HHS are shown in the table (table 1) [1].

- In DKA, metabolic acidosis is often the major finding, while the serum glucose concentration is generally below 800 mg/dL (44.4 mmol/L) and often in the 350 to 500 mg/dL (19.4 to 27.8 mmol/L) range [1-3]. However, serum glucose concentrations may exceed 900 mg/dL (50 mmol/L) in patients with DKA, most of whom are comatose [3,4], or may be normal or minimally elevated (<250 mg/dL [13.9 mmol/L]) in patients with euglycemic DKA (which occurs more often in patients with poor oral intake, those treated with insulin prior to arrival in the emergency department, pregnant women, those who use sodium-glucose cotransporter 2 [SGLT2] inhibitors, and insulin pump-treated patients in whom insulin delivery is interrupted due to catheter or pump failure).

- In HHS, there is little or no ketoacid accumulation, the serum glucose concentration frequently exceeds 1000 mg/dL (56 mmol/L), the plasma osmolality (Posm) may reach 380 mOsmol/kg, and neurologic abnormalities are frequently present (including coma in 25 to 50 percent of cases) [1,2,5,6].

The typical total body deficits of water and electrolytes in DKA and HHS are compared in the table (table 2). (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum glucose' and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Diagnostic criteria'.)

TREATMENT

Overview and protocols — The treatment of DKA (algorithm 1) and HHS (algorithm 2) is similar, including correction of the fluid and electrolyte abnormalities that are typically present (hyperosmolality, hypovolemia, metabolic acidosis [in DKA], and potassium depletion) and the administration of insulin [1,7-9].

- **Correction of fluid and electrolyte abnormalities** – The first step in the treatment of DKA or HHS is infusion of isotonic saline to expand extracellular volume and stabilize cardiovascular status (table 3). This also increases insulin responsiveness by lowering the plasma osmolality (Posm), reducing vasoconstriction and improving perfusion, and

reducing stress hormone levels [10,11]. The next step is correction of the potassium deficit (if present). The choice of fluid replacement should be influenced by the potassium deficit. The osmotic effect of potassium repletion must be considered since potassium is as osmotically active as sodium. (See 'Fluid replacement' below and 'Potassium replacement' below.)

- **Administration of insulin** – Low-dose intravenous (IV) insulin should be administered to all patients with moderate to severe DKA who have a serum potassium ≥3.3 mEq/L. If the serum potassium is less than 3.3 mEq/L, insulin therapy should be delayed until potassium replacement has begun and the serum potassium concentration has increased. The delay is necessary because insulin will worsen the hypokalemia by driving potassium into the cells, and this could trigger cardiac arrhythmias. IV regular insulin and rapid-acting insulin analogs are equally effective in treating DKA. (See 'Insulin' below.)

Therapy requires frequent clinical and laboratory monitoring and the identification and treatment of any precipitating events, including infection. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which can precipitate DKA, should be discontinued. Permanent discontinuation of the SGLT2 inhibitor should be strongly considered. (See 'Monitoring' below and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Precipitating factors'.)

Our approach outlined below is based upon clinical experience and is largely in agreement with the American Diabetes Association (ADA) consensus algorithms for the treatment of DKA (algorithm 1) and HHS (algorithm 2) and the Joint British Diabetes Societies guideline for the management of DKA [1,12,13].

Fluid replacement — In patients with DKA or HHS, we recommend IV electrolyte and fluid replacement to correct both hypovolemia and hyperosmolality. Fluid repletion may be initiated with isotonic saline (0.9 percent sodium chloride [NaCl]) or isotonic buffered crystalloid (eg, Lactated Ringer). Patients with euglycemic DKA generally require both insulin and glucose to treat the ketoacidosis and prevent hypoglycemia, respectively, and in such patients, dextrose is added to IV fluids at the initiation of therapy. For patients with a more classic presentation of hyperglycemic DKA, we add dextrose to the saline solution when the serum glucose declines to 200 mg/dL (11.1 mmol/L) in DKA (algorithm 1) or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS (algorithm 2).

No trials have directly compared saline with buffered crystalloid administration specifically in patients with DKA. In a subgroup analysis of two cluster-randomized trials evaluating choice of isotonic fluid in an emergency or critical care setting, adults with DKA who received buffered

crystalloids (n = 94) had a shorter time to DKA resolution compared with those who received saline (n = 78; median 13 versus 16.9 hours, respectively) [14].

The optimal rate of initial isotonic saline infusion is dependent upon the clinical state of the patient:

- In patients with hypovolemic shock, isotonic saline should initially be infused as quickly as possible. (See "Treatment of severe hypovolemia or hypovolemic shock in adults".)
- In hypovolemic patients without shock or heart failure, isotonic saline is infused at a rate of 15 to 20 mL/kg lean body weight per hour (approximately 1000 mL/hour in an average-sized person) for the first couple of hours, with a maximum of <50 mL/kg in the first four hours (algorithm 1 and algorithm 2) [1].
- In euvolemic patients, isotonic saline is infused at a lower rate, guided by clinical assessment.

After the second or third hour, optimal fluid replacement depends upon the state of hydration, serum electrolyte levels, and the urine output. The most appropriate IV fluid composition is determined by the sodium concentration "corrected" for the degree of hyperglycemia. The "corrected" sodium concentration can be approximated by adding 2 mEq/L to the plasma sodium concentration for each 100 mg/100 mL (5.5 mmol/L) increase above normal in glucose concentration (calculator 1).

If the "corrected" serum sodium concentration is [1]:

- Less than 135 mEq/L, isotonic saline should be continued at a rate of approximately 250 to 500 mL/hour
- Normal or elevated, the IV fluid is generally switched to one-half isotonic saline at a rate of 250 to 500 mL/hour in order to provide electrolyte-free water

The timing of one-half isotonic saline therapy may also be influenced by the need for potassium replacement. Potassium salts have an osmotic effect equivalent to sodium salts, and adding potassium to isotonic fluids generates a hypertonic solution. Thus, significant potassium replacement may be another indication for the use of one-half isotonic saline. (See 'Potassium replacement' below.)

Correction of the hyperosmolar state may enhance the response to low-dose insulin therapy [10,11]. Adequacy of fluid replacement is judged by frequent hemodynamic and laboratory monitoring (see 'Monitoring' below). In patients with abnormal renal or cardiac function, more

frequent monitoring must be performed to avoid iatrogenic fluid overload [8,9,11,15-18]. The goal is to correct estimated deficits (table 2) within the first 24 hours. However, osmolality should not be reduced too rapidly, because this may generate cerebral edema. (See 'Cerebral edema' below and "Diabetic ketoacidosis in children: Treatment and complications", section on 'Cerebral injury'.)

Potassium replacement — Potassium replacement is initiated immediately if the serum potassium is ≤5.3 mEq/L, provided urine output is adequate (approximately >50 mL/hour) (algorithm 1). Almost all patients with DKA or HHS have a substantial potassium deficit, usually due to urinary losses generated by the glucose osmotic diuresis and secondary hyperaldosteronism. Despite the total body potassium deficit, the serum potassium concentration is usually normal or, in approximately one-third of cases, elevated at presentation. This is largely due to insulin deficiency and hyperosmolality, each of which cause potassium movement out of the cells [19].

- If the initial serum potassium is below 3.3 mEq/L, insulin should not be administered until the potassium has been raised above this threshold. IV potassium chloride (KCl; 20 to 40 mEq/hour, which usually requires 20 to 40 mEq/L added to saline) should be given. The choice of replacement fluid (isotonic or one-half isotonic saline) depends upon the state of hydration, corrected sodium concentration, dose of KCl, blood pressure, and a clinical assessment of overall volume status. Patients with marked hypokalemia require aggressive potassium replacement (40 mEq/hour, with additional supplementation based upon hourly serum potassium measurements) to raise the serum potassium concentration above 3.3 mEq/L [20-22].

- If the initial serum potassium is 3.3 to 5.3 mEq/L, IV KCl (20 to 30 mEq) is added to each liter of IV replacement fluid. Adjust potassium replacement to maintain the serum potassium concentration in the range of 4 to 5 mEq/L.

- If the initial serum potassium concentration is greater than 5.3 mEq/L, then potassium replacement should be delayed until the serum concentration has fallen below this level.

Potassium salts added to IV fluids have the same osmotic effect as sodium salts, and this should be considered when determining the potential impact of IV fluid infusion on osmolality. As an example, 40 mEq of KCl added to 1 L of fluid generates 80 mOsmol/L of electrolyte osmolarity. The addition of 40 mEq of potassium to 1 L of one-half isotonic saline creates a solution with an osmolarity of 234 mOsmol/L (77 mEq NaCl and 40 mEq KCl), which is osmotically equal to three-quarters isotonic saline. (The osmolarity of isotonic saline is 308 mOsmol/L.) If 40 mEq of KCl is added to isotonic saline, the final osmolarity will be approximately 388 mOsmol/L. However, KCl

will not have the same extracellular fluid (ECF) expansion effect as NaCl, because most of the potassium will shift into cells very rapidly. (See "Maintenance and replacement fluid therapy in adults", section on 'Choice of replacement fluid'.)

The altered potassium distribution is rapidly reversed with the administration of insulin and can result in an often dramatic fall in the serum potassium concentration, despite potassium replacement [20,21]. However, potassium replacement must be done cautiously if renal function remains depressed and/or urine output does not increase to a level >50 mL/hour. Careful monitoring of the serum potassium is essential for the management of both DKA and HHS. (See 'Monitoring' below and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis", section on 'Potassium'.)

Insulin — We recommend initiating treatment with low-dose IV insulin in all patients with moderate to severe DKA or HHS who have a serum potassium ≥3.3 mEq/L. The only indication for delaying the initiation of insulin therapy is if the serum potassium is below 3.3 mEq/L since insulin will worsen the hypokalemia by driving potassium into the cells. Patients with an initial serum potassium below 3.3 mEq/L should receive fluid and potassium replacement prior to treatment with insulin. Insulin therapy should be delayed until the serum potassium is ≥3.3 mEq/L to avoid complications such as cardiac arrhythmias, cardiac arrest, and respiratory muscle weakness [1,20,21]. (See 'Fluid replacement' above and 'Potassium replacement' above.)

IV regular insulin and rapid-acting insulin analogs are equally effective in treating DKA [23]. The choice of IV insulin is based upon institutional preferences, clinician experience, and cost concerns. We generally prefer regular insulin, rather than rapid-acting insulin analogs, due to its much lower cost. For acute management of DKA or HHS, there is no role for long- or intermediate-acting insulin; however, long-acting (glargine, detemir) or intermediate-acting (NPH) insulin is administered after recovery from ketoacidosis, prior to discontinuation of IV insulin, to ensure adequate insulin levels after IV insulin is discontinued. In this setting, we do not use degludec or ultra-long-acting U-300 insulin glargine (given their long half-life) as it will take at least three to four days to reach steady state [24]. In patients with mild DKA (particularly in patients with mild DKA due to rationed or missed doses of basal insulin), intermediate- or long-acting insulin can be administered at the initiation of treatment, along with rapid-acting insulin. (See 'Intravenous regular insulin' below and 'Converting to subcutaneous insulin' below and 'Intravenous insulin analogs' below and 'Subcutaneous insulin regimens' below.)

Insulin therapy lowers the serum glucose concentration (by decreasing hepatic glucose production, the major effect, and enhancing peripheral utilization, a less important effect [25]), diminishes ketone production (by reducing both lipolysis and glucagon secretion), and may augment ketone utilization. Inhibition of lipolysis requires a much lower level of insulin than

that required to reduce the serum glucose concentration. Therefore, if the administered dose of insulin is reducing the glucose concentration, it should be more than enough to stop ketone generation [8,25,26]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis", section on 'Pathogenesis'.)

Intravenous regular insulin — In HHS or moderate to severe DKA, treatment can be initiated with an IV bolus of regular insulin (0.1 units/kg body weight) in order to raise insulin levels rapidly, followed within five minutes by a continuous infusion of regular insulin of 0.1 units/kg per hour (equivalent to 7 units/hour in a 70-kg patient) [8,27-30]. Alternatively, the bolus dose can be omitted if a higher dose of continuous IV regular insulin (0.14 units/kg per hour, equivalent to 10 units/hour in a 70-kg patient) is initiated [31]. The insulin dosing is the same in DKA and HHS (algorithm 1 and algorithm 2). The possible role of other insulin preparations is discussed below. (See 'Intravenous insulin analogs' below and 'Subcutaneous insulin regimens' below.)

These doses of IV regular insulin usually decrease the serum glucose concentration by approximately 50 to 70 mg/dL (2.8 to 3.9 mmol/L) per hour [25,28-30]. Higher doses do not generally produce a more prominent glucose-lowering effect, probably because the insulin receptors are fully saturated and activated by the lower doses [27]. However, if the serum glucose does not fall by at least 50 to 70 mg/dL (2.8 to 3.9 mmol/L) from the initial value in the first hour, check the IV access to be certain that the insulin is being delivered and that no IV line filters that may bind insulin have been inserted into the line. After these possibilities are eliminated, the insulin infusion rate should be doubled every hour until a steady decline in serum glucose of this magnitude is achieved.

The fall in serum glucose is the result of both insulin activity and the beneficial effects of volume repletion. Volume repletion alone can initially reduce the serum glucose by 35 to 70 mg/dL (1.9 to 3.9 mmol/L) per hour due to the combination of ECF expansion; reduction of plasma osmolality; increased urinary losses resulting from improved renal perfusion and glomerular filtration; and a reduction in the levels of "stress hormones," which oppose the effects of insulin [16,29]. The serum glucose levels often fall more rapidly in patients with HHS who are typically more volume depleted.

When the serum glucose approaches 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS, switch the IV saline solution to 5 percent dextrose in saline and attempt to decrease the insulin infusion rate to 0.02 to 0.05 units/kg per hour [9,11,27]. If possible, do not allow the serum glucose at this time to fall below 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS, because this may promote the

development of cerebral edema. (See 'Cerebral edema' below and "Diabetic ketoacidosis in children: Cerebral injury (cerebral edema)".)

Intravenous insulin analogs — There is no advantage of rapid-acting or ultra-rapid-acting insulin analogs over regular insulin. Intravenous regular insulin and glulisine insulin are equally effective and equipotent for the treatment of DKA [23]. (See "General principles of insulin therapy in diabetes mellitus", section on 'Human insulins'.)

Subcutaneous insulin regimens — Patients with mild DKA (table 1) can be safely treated with subcutaneous, rapid-acting insulin analogs on a general medical floor or in the emergency department but only when adequate staffing is available to carefully monitor the patient and check capillary blood glucose with a reliable glucose meter, typically every hour. We do not recommend the use of continuous glucose monitoring (CGM) in this situation, as it has not been studied.

Subcutaneous insulin protocols are being used with increasing frequency to treat selected patients with mild to moderate DKA during the **COVID-19 pandemic**, when intravenous insulin may not be practical owing to the need to limit frequency of contact of staff with patients. In this setting, dosing and monitoring are performed every two to four hours. (See "COVID-19: Issues related to diabetes mellitus in adults", section on 'DKA/HHS'.)

Treatment of DKA with subcutaneous insulin has not been evaluated in severely ill patients. In mild DKA, direct comparison of intramuscular, subcutaneous, and IV insulin therapy for hemodynamically stable DKA patients shows similar efficacy and safety [32-36]. In addition, subcutaneous administration of rapid-acting insulin analogs (eg, insulin lispro, aspart) given every one or two hours has been demonstrated to be safe in two randomized trials in adults with uncomplicated DKA (algorithm 1) [33,34]. In one trial, for example, 40 patients with DKA were assigned to one of two regimens [33]:

- Subcutaneous, rapid-acting insulin lispro as an initial injection of 0.3 units/kg, followed by 0.1 units/kg every hour until the serum glucose was less than 250 mg/dL (13.9 mmol/L). The insulin lispro dose was then decreased to 0.05 to 0.1 units/kg and administered every one or two hours until resolution of the ketoacidosis. These patients were treated on a regular internal medicine floor or in an intermediate care unit.

- IV regular insulin as an initial bolus of 0.1 units/kg, followed by an infusion of 0.1 units/kg per hour until the serum glucose was less than 250 mg/dL (13.9 mmol/L). The insulin dose was then decreased to 0.05 to 0.1 units/kg per hour until resolution of the ketoacidosis. These patients were treated in the intensive care unit.

The duration of therapy until correction of hyperglycemia and resolution of ketoacidosis was the same with both regimens (7 and 10 to 11 hours, respectively), but there was a 39 percent reduction in cost with insulin lispro, mainly related to the higher cost of treatment in the intensive care unit.

Bicarbonate and metabolic acidosis — Although the indications for sodium bicarbonate therapy to help correct metabolic acidosis are controversial, there are selected patients who may benefit from cautious alkali therapy [37]. They include:

- Patients with an arterial pH <6.9 in whom decreased cardiac contractility and vasodilatation can impair tissue perfusion [38,39]. At an arterial pH above 7.0, most experts agree that bicarbonate therapy is not necessary since therapy with insulin and volume expansion will largely reverse the metabolic acidosis [40].

  For patients with pH <6.9, we give 100 mEq of sodium bicarbonate in 400 mL sterile water administered over two hours. If the serum potassium is less than 5.3 mEq/L, we add 20 mEq of KCl. When the bicarbonate concentration increases, the serum potassium may fall and more aggressive KCl replacement may be required.

- Patients with potentially life-threatening hyperkalemia, since bicarbonate administration in acidemic patients may drive potassium into cells, thereby lowering the serum potassium concentration. The exact potassium level that should trigger this intervention has not been defined; we administer sodium bicarbonate if the potassium level is >6.4 mEq/L [41]. (See "Treatment and prevention of hyperkalemia in adults".)

The venous pH and bicarbonate concentration should be monitored every two hours, and bicarbonate doses can be repeated until the pH rises above 7.0. (See 'Monitoring' below.)

The indications for bicarbonate therapy in DKA are controversial [42], and evidence of benefit is lacking [43-45]. In a randomized trial of 21 DKA patients with an admission arterial pH between 6.90 and 7.14 (mean 7.01), bicarbonate therapy did not change morbidity or mortality [43]. However, the study was small, limited to patients with an arterial pH 6.90 and above, and there was no difference in the rate of rise in the arterial pH and serum bicarbonate between the bicarbonate and placebo groups. No prospective randomized trials have been performed concerning the use of bicarbonate in DKA with pH values less than 6.90.

Bicarbonate administration is also controversial because, in addition to lack of evidence for benefit, there are several potential harmful effects:

- If bicarbonate infusion successfully increases the blood bicarbonate concentration, this can reduce the hyperventilatory drive, which will raise the blood partial pressure of carbon dioxide (pCO_2). Increased blood carbon dioxide (CO_2) tension is more quickly reflected across the blood brain barrier than the increased arterial bicarbonate. This may cause a paradoxical fall in cerebral pH. Although neurologic deterioration has been attributed to this mechanism, it remains a very controversial effect and, if it occurs, is rare [37].

- The administration of alkali may slow the rate of recovery of the ketosis [46,47]. In a study of seven patients, the three patients treated with bicarbonate had a rise in serum ketoacid anion levels and a six-hour delay in resolution of ketosis [46]. Animal studies indicate that bicarbonate infusion can accelerate ketogenesis. This is thought to be related to the fact that acidemia has a "braking effect" on organic acid generation. This brake is lessened by any maneuver that increases systemic pH [43].

- Alkali administration can lead to a post-treatment metabolic alkalosis since metabolism of ketoacid anions with insulin results in the generation of bicarbonate and spontaneous correction of most of the metabolic acidosis. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis", section on 'Anion gap metabolic acidosis'.)

Phosphate depletion — Based upon the observations described below, we do **not** recommend the routine use of phosphate replacement in the treatment of DKA or HHS. However, phosphate replacement should be strongly considered if severe hypophosphatemia occurs (serum phosphate concentration below 1 mg/dL or 0.32 mmol/L), especially if cardiac dysfunction, hemolytic anemia, and/or respiratory depression develop [48-52]. When needed, potassium or sodium phosphate 20 to 30 mEq can be added to 1 L of IV fluid.

Although whole-body phosphate depletion is common in uncontrolled diabetes mellitus, the serum phosphate concentration may initially be normal or elevated due to movement of phosphate out of the cells [7,49]. Similar to potassium, phosphate depletion and hypophosphatemia may be rapidly unmasked following the institution of insulin therapy and IV volume expansion. This frequently leads to asymptomatic hypophosphatemia, which gradually resolves. (See "Hypophosphatemia: Clinical manifestations of phosphate depletion".)

Prospective, randomized trials of patients with DKA have failed to show a beneficial effect of phosphate replacement on the duration of ketoacidosis; dose of insulin required; or the rate of fall of serum glucose, morbidity, or mortality [53-55]. In addition, phosphate replacement may have adverse effects, such as hypocalcemia and hypomagnesemia [53,56-58]. Consequently,

routine replacement is not indicated. When the patient stabilizes, phosphate-rich food such as dairy products and almonds may be recommended.

MONITORING

General — The serum glucose should initially be measured every hour until stable, while serum electrolytes, blood urea nitrogen (BUN), creatinine, and venous pH (for DKA) should be measured every two to four hours, depending upon disease severity and the clinical response [1,9]. In-patient serum glucose measurement should be done with hospital-approved bedside devices or in the chemistry laboratory and not with continuous glucose monitoring (CGM) devices.

The effective plasma osmolality (effective Posm) or tonicity can be estimated from the sodium and glucose concentrations using the following equations, depending upon the units for sodium (Na) and glucose:

Effective Posm = [2 x Na (mEq/L)] + [glucose (mg/dL) ÷ 18]

Effective Posm = [2 x Na (mmol/L)] + glucose (mmol/L)

The Na in these equations is the actual measured plasma sodium concentration and not the "corrected" sodium concentration.

It is strongly suggested that a flow sheet of laboratory values and clinical parameters be utilized because it allows better visualization and evaluation of the clinical picture throughout treatment of DKA (form 1).

Monitoring with arterial blood gases is unnecessary during the treatment of DKA; venous pH, which is approximately 0.03 units lower than arterial pH [59], is adequate to assess the response to therapy and avoids the pain and potential complications associated with repeated arterial punctures. If blood chemistry results are promptly available, an alternative to monitoring venous pH is to monitor the serum bicarbonate concentration (to assess correction of the metabolic acidosis) and the serum anion gap (to assess correction of the ketoacidemia).

Where available, bedside ketone meters that measure capillary blood beta-hydroxybutyrate are an alternative to the measurement of electrolytes and anion gap for monitoring the response to treatment. These devices are increasingly available, reliable, and convenient [13]. Beta-hydroxybutyrate can then be measured every two hours depending on the clinical response [60]. When bedside meters are not available, monitoring venous pH and/or the venous bicarbonate and anion gap is sufficient.

Resolution of DKA/HHS — The hyperglycemic crisis is considered to be resolved when the following goals are reached:

- The ketoacidosis has resolved, as evidenced by normalization of the serum anion gap (less than 12 mEq/L) and, when available, blood beta-hydroxybutyrate levels
- Patients with HHS are mentally alert and the effective plasma osmolality has fallen below 315 mOsmol/kg
- The patient is able to eat

The disappearance of ketoacid anions in the serum and correction of the ketoacidosis can be monitored by measuring venous pH, beta-hydroxybutyrate directly, and/or serum electrolytes and bicarbonate concentrations with calculation of the serum anion gap. The serum anion gap provides an estimate of the quantity of unmeasured anions in the plasma. It is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium). The sodium concentration used for this calculation is the concentration reported by the laboratory not the "corrected" sodium concentration.

Accumulation of ketoacid anions (the sum of beta-hydroxybutyrate and acetoacetate) increases the anion gap above its baseline, and the increment reflects the sum of their concentrations in serum. Monitoring the anion gap will provide a reasonable estimate of changes in these serum ketoacid anion concentrations. The anion gap returns to the normal range when ketoacid anions have disappeared from the serum.

Correction of the ketoacidosis can also be monitored by direct measurement of serum or capillary beta-hydroxybutyrate. Although assessments of urinary or serum ketone levels by the nitroprusside method can be used for the initial diagnosis of ketoacidosis, it should **not** be used for monitoring resolution of DKA. Nitroprusside reacts mainly with acetoacetate, to a much lesser degree with acetone (which is not an acid), and not with beta-hydroxybutyrate. These characteristics of this test can generate clinical confusion. For example, a positive nitroprusside test may persist for up to 36 hours after resolution of the ketoacidosis due to a positive reaction with acetone, which is slowly eliminated, mainly via the lungs [61,62]. Since acetone is not an acid, a persistent nitroprusside reaction due to acetone does not indicate ketoacidosis. In addition, active treatment of ketoacidosis shifts the reaction between beta-hydroxybutyrate and acetoacetate toward acetoacetate. This may result in an increasingly positive nitroprusside test (due to higher acetoacetate concentrations) despite an overall improvement of the ketoacidosis (figure 1) [26].

In the absence of severe kidney disease, almost all patients develop a normal anion gap acidosis ("non-gap" or "hyperchloremic acidosis") during the resolution phase of the ketoacidosis. This occurs because aggressive intravenous (IV) volume expansion reverses volume contraction and improves renal function, which accelerates the loss of ketoacid anions with sodium and potassium [63,64]. The loss of these ketoacid anion salts into the urine represent "potential" bicarbonate loss from the body. Insulin therapy will have no further effect on the acidosis when this stage evolves. The hyperchloremic acidosis will slowly resolve as the kidneys excrete ammonium chloride (NH_4Cl) and regenerate bicarbonate.

Converting to subcutaneous insulin — For patients with DKA, we initiate a multiple-dose (**basal-bolus**), subcutaneous insulin schedule when the ketoacidosis has resolved and the patient is able to eat (see 'Resolution of DKA/HHS' above). If the patient is unable to eat, it is preferable to continue the IV insulin infusion. For patients with HHS, IV insulin infusion can be tapered and a multiple-dose (basal-bolus), subcutaneous insulin schedule started when the serum glucose falls below 250 to 300 mg/dL (13.9 to 16.7 mmol/L).

The most convenient time to transition to subcutaneous insulin is before a meal. The IV insulin infusion should be continued for two to four hours after initiating the short- or rapid-acting subcutaneous insulin because abrupt discontinuation of IV insulin acutely reduces insulin levels and may result in recurrence of hyperglycemia and/or ketoacidosis. Basal insulin (NPH, U-100 glargine, or detemir) can be administered either (a) at the same time as the first injection of rapid-acting insulin, or (b) earlier (for example, the previous evening), along with a decrease in the rate of IV insulin infusion. We typically do not administer degludec or U-300 glargine as the basal insulin when transitioning from IV insulin due to its very long half-life, and subsequently, the time it takes to reach steady state (two to three days).

For patients with known diabetes who were previously being treated with insulin, their pre-DKA or pre-HHS insulin regimen may be restarted. For patients who are treated with continuous subcutaneous insulin infusion (insulin pump), the previous basal rate can be resumed. However, if the IV insulin requirements are significantly higher than their usual insulin requirements, it is reasonable to increase the basal rate temporarily. For those using partially automated insulin delivery (hybrid closed-loop) systems, it is also reasonable to stay in "manual mode" for the first 24 to 48 hours while insulin requirements return to baseline. If automated insulin delivery is immediately resumed, blood glucose levels likely will be higher for the first few days.

In patients with new-onset type 1 diabetes who have presented with DKA, an initial total daily dose (TDD) of 0.5 to 0.8 units/kg units of insulin per day is reasonable, until an optimal dose is established. Approximately 40 to 50 percent of the TDD should be given as a basal insulin, either as once- or twice-daily U-100 glargine or detemir, or as twice-daily intermediate-acting

insulin (NPH). The long-acting insulin can be given either at bedtime or in the morning; the NPH is usually given as approximately two-thirds of the dose in the morning and one-third at bedtime. The remainder of the TDD is given as short-acting or rapid-acting insulin, divided before meals. The pre-meal dosing is determined by the pre-meal glucose level, meal size, and content, glucose trends (when available from CGM), as well as activity and exercise pattern. If NPH is the basal insulin used, a mid-day (pre-lunch) rapid-acting insulin may not be necessary. Good clinical judgment and frequent glucose assessment are vital in initiating a new insulin regimen in insulin-naive patients. Most importantly, the regimen needs to be adjusted based on empiric results provided by glucose monitoring and responsive to individual lifestyle patterns including eating and activity and exercise patterns. (See "General principles of insulin therapy in diabetes mellitus" and "Management of blood glucose in adults with type 1 diabetes mellitus", section on 'Designing an MDI insulin regimen' and "Insulin therapy in type 2 diabetes mellitus".)

COMPLICATIONS

Hypoglycemia and hypokalemia are the most common complications of the treatment of DKA and HHS. These complications have become much less common since low-dose intravenous (IV) insulin treatment and careful monitoring of serum potassium have been implemented [65]. Hyperglycemia may recur from interruption or discontinuation of IV insulin without adequate overlap coverage with subcutaneous insulin.

Cerebral edema — Cerebral edema in uncontrolled diabetes mellitus (usually DKA, with only occasional reports in HHS) is primarily a disease of children, and almost all affected patients are younger than 20 years old [66]. Symptoms typically emerge within 12 to 24 hours of the initiation of treatment for DKA but may exist prior to the onset of therapy. Issues related to cerebral edema in DKA, including pathogenesis, are discussed in detail separately in the pediatric section but will be briefly reviewed here. (See "Diabetic ketoacidosis in children: Cerebral injury (cerebral edema)".)

Headache is the earliest clinical manifestation, followed by lethargy and decreased arousal. Neurologic deterioration may be rapid. Seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest can develop. Symptoms progress if brainstem herniation occurs, and the rate of progression may be so rapid that clinically recognizable papilledema does not develop.

DKA-associated cerebral edema has a mortality rate of 20 to 40 percent [1]. Thus, careful monitoring for changes in mental or neurologic status that would permit early identification and therapy of cerebral edema is essential.

The 2009 American Diabetes Association (ADA) guidelines on hyperglycemic crises in diabetes in adults suggested that the following preventive measures may reduce the risk of cerebral edema in high-risk patients [1]:

- Gradual replacement of sodium and water deficits in patients who are hyperosmolar. The usual IV fluid regimen during the first few hours of treatment is isotonic saline at a rate of 15 to 20 mL/kg lean body weight per hour (approximately 1000 mL/hour in an average-sized person) with a maximum of <50 mL/kg in the first two to three hours (algorithm 1 and algorithm 2).

- Dextrose should be added to the saline solution once the serum glucose levels have fallen to 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS. In patients with HHS, the serum glucose should be maintained at 250 to 300 mg/dL (13.9 to 16.7 mmol/L) until the hyperosmolality and mental status improve and the patient is clinically stable.

Data evaluating the outcome and treatment of cerebral edema in adults are not available. Recommendations for treatment are based upon clinical judgment in the absence of scientific evidence. Case reports and small series in children suggest benefit from prompt administration of mannitol (0.25 to 1 g/kg) and perhaps from hypertonic (3 percent) saline (5 to 10 mL/kg over 30 min) [66]. These interventions raise the plasma osmolality (Posm) and generate an osmotic movement of water out of brain cells and a reduction in cerebral edema.

Noncardiogenic pulmonary edema — Hypoxemia and rarely noncardiogenic pulmonary edema can complicate the treatment of DKA [67-70]. Hypoxemia is attributed to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance [11]. Patients with DKA who are found to have a wide alveolar-arterial oxygen gradient and/or rales may be at higher risk for the development of pulmonary edema.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hyperglycemic emergencies".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Diabetic ketoacidosis (The Basics)" and "Patient education: Hyperosmolar hyperglycemic state (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **General principles** – The treatment of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) is similar and involves correction of the fluid and electrolyte abnormalities that are typically present, including hyperosmolality, hypovolemia, metabolic acidosis (in DKA), and potassium depletion, and the administration of insulin (table 3 and algorithm 1 and algorithm 2). Frequent monitoring is essential, and underlying precipitating events should be identified and corrected. (See 'Overview and protocols' above.)

- **Fluid replacement** – Individuals with DKA or HHS require intravenous (IV) fluid replacement to correct both hypovolemia and hyperosmolality. Isotonic saline and isotonic buffered crystalloid (eg, Lactated Ringer) are both reasonable options. The optimal rate is guided by clinical assessment.

  Fluid replacement should correct estimated volume deficits within the first 24 hours, with care to avoid an overly rapid reduction in the serum osmolality. (See 'Fluid replacement' above.)

  - **Hypovolemia with shock** – Isotonic crystalloid (saline or buffered crystalloids) should be infused as quickly as possible in patients with hypovolemic shock. (See "Treatment of severe hypovolemia or hypovolemic shock in adults", section on 'Nonhemorrhagic shock'.)

- **Hypovolemia without shock** – In hypovolemic patients without shock or heart failure, we suggest isotonic (0.9 percent) saline infused at a rate of 15 to 20 mL/kg per hour (approximately 1000 mL/hour in an average-sized person) for the first couple of hours (**Grade 2C**) . This is followed by one-half isotonic (0.45 percent) saline at a rate of approximately 250 to 500 mL/hour if the serum sodium (corrected for hyperglycemia) is normal or elevated; isotonic saline is continued at a rate of approximately 250 to 500 mL/hour if the serum sodium (corrected for hyperglycemia) is low.

  The need for potassium repletion may influence the timing of one-half isotonic saline therapy since the addition of potassium to isotonic saline creates a hypertonic solution that can worsen the underlying hyperosmolality. (See 'Potassium replacement' above.)

- **Euvolemia** – Isotonic saline is infused at a lower rate than in hypovolemic patients without shock, guided by clinical assessment.

- **Potassium replacement** – Most patients with DKA or HHS require IV potassium replacement. The dose depends on the initial serum potassium level (algorithm 1 and algorithm 2). In patients with high potassium (>5.3 mEq/L) and/or low urine output (eg, <50 mL/hour), potassium replacement should be delayed until potassium is ≤5.3 mEq/L and urine output ≥50 mL/hour.

  Most patients with DKA or HHS have a substantial potassium deficit (due to urinary losses and secondary hyperaldosteronism) that may not be reflected in serum levels. (See 'Fluid replacement' above and 'Potassium replacement' above.)

- **Insulin** – In patients with initial serum potassium <3.3 mEq/L, insulin therapy should be delayed until the serum potassium is ≥3.3 mEq/L to avoid complications of hypokalemia. Aggressive potassium replacement is needed to avoid further delay in insulin therapy with increased risk of progressive acidosis (algorithm 1).

  Insulin dosing is titrated based on hourly glucose measurement. We add dextrose to the IV fluids when the serum glucose approaches 200 mg/dL (11.1 mmol/L) in DKA or 250 to 300 mg/dL (13.9 to 16.7 mmol/L) in HHS. In patients with euglycemic DKA, we add dextrose to the IV fluids at the initiation of therapy. (See 'Fluid replacement' above.)

  - **HHS or moderate to severe DKA** – Patients with HHS or with moderate to severe DKA and a serum potassium ≥3.3 mEq/L require intensive insulin therapy (intravenous insulin infusion).

We suggest IV regular insulin rather than rapid-acting insulin analogs (eg, insulin lispro, aspart, and glulisine) (**Grade 2C**), due to similar efficacy and much lower cost. The initial insulin dose is the same in DKA and HHS (algorithm 1 and algorithm 2). Once serum potassium is ≥3.3 mEq/L, we give a continuous IV infusion of regular insulin at 0.14 units/kg per hour; at this dose, an initial IV bolus is not necessary. An alternative is to administer an IV bolus (0.1 units/kg body weight) of regular insulin, followed by a continuous infusion at a dose of 0.1 units/kg per hour. The dose is doubled if the glucose does not fall by 50 to 70 mg/dL (2.8 to 3.9 mmol/L) in the first hour. (See 'Insulin' above.)

- **Mild DKA** – For patients with mild DKA (table 1), IV regular insulin or subcutaneous rapid-acting insulin analogs are options for initial treatment. Subcutaneous administration of insulin is safe only when adequate staffing is available to allow for close patient monitoring and frequent capillary blood glucose measurement with a reliable glucose meter, typically every hour. (See 'Subcutaneous insulin regimens' above.)

- **Indications for bicarbonate** – For most patients with DKA, we suggest **not** giving sodium bicarbonate (**Grade 2C**). However, in patients with severe acidosis (arterial pH <6.9), bicarbonate administration is reasonable. (See 'Bicarbonate and metabolic acidosis' above.)

- **Indications for phosphate** – For most patients, we suggest **not** administering phosphate (**Grade 2B**). Whole-body phosphate depletion is usually present, but routine phosphate administration does not appear to have clear benefit and can be associated with hypocalcemia and hypomagnesemia.

  However, patients with severe hypophosphatemia (<1 mg/dL [0.32 mmol/L]) should receive phosphate. (See 'Phosphate depletion' above.)

- **Monitoring** – Monitoring involves hourly glucose measurement until stable and basic chemistry profile and venous pH (for DKA) every two to four hours. The course of ketoacidemia can be assessed by direct measurement of beta-hydroxybutyrate, the major circulating ketoacid, and/or measurement of the serum anion gap. In contrast, nitroprusside tablets or reagent sticks should not be used, because they react with acetoacetate and acetone but not with beta-hydroxybutyrate. Acetone is not an acid and does not generate metabolic acidosis. (See 'Monitoring' above.)

- **Potential complications** – Cerebral edema is rare in adults but is associated with high rates of morbidity and mortality. Possible preventive measures in high-risk patients

include gradual rather than rapid correction of fluid and sodium deficits (maximum reduction in plasma osmolality [Posm] of 3 mOsmol/kg per hour), and maintenance of a slightly elevated serum glucose until the patient is stable. (See 'Cerebral edema' above.)

- **Converting to subcutaneous insulin** – We initiate a multiple-dose (basal-bolus), subcutaneous insulin schedule when the ketoacidosis has resolved and the patient is able to eat. For patients with HHS, IV insulin infusion can be tapered and a multiple-dose, subcutaneous insulin schedule started when the serum glucose falls below 250 to 300 mg/dL (13.9 to 16.7 mmol/L). The IV insulin infusion should be continued for two to four hours after initiating the subcutaneous insulin to avoid recurrence of hyperglycemia. When converting to subcutaneous insulin, we do not use ultra-long-acting insulins (eg, degludec, U-300 glargine) as the basal insulin; these have a long half-life and require two to three days to reach steady state. (See 'Converting to subcutaneous insulin' above.)

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Topic 1795 Version 53.0

GRAPHICS

Typical laboratory characteristics of diabetic ketoacidosis and hyperosmolar hyperglycemic state*

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Plasma glucose (mmol/L)	>13.9	>13.9	>13.9	>33.3
Arterial pH	7.25 to 7.30	7.00 to 7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15 to 18	10 to <15	<10	>18
Urine ketones¶	Positive	Positive	Positive	Small
Serum ketones – Nitroprusside reaction	Positive	Positive	Positive	≤ Small
Serum ketones – Enzymatic assay of beta hydroxybutyrate (normal range <0.6 mmol/L)Δ	3 to 4 mmol/L	4 to 8 mmol/L	>8 mmol/L	<0.6 mmol/L
Effective serum osmolality (mOsm/kg)◇	Variable	Variable	Variable	>320
Anion gap§	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state.

* There may be considerable diagnostic overlap between DKA and HHS.

¶ Nitroprusside reaction method.

Δ Many assays for beta hydroxybutyrate can only report markedly elevated values as >6.0 mmol/L.

◇ Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.

§ Calculation: (Na+) – (Cl– + HCO3–) (mEq/L).

Graphic 72111 Version 9.0

Typical total body deficits of water and electrolytes in diabetic ketoacidosis an hyperosmolar hyperglycemic state*

	DKA	HHS
Total water (L)	6	9
Water (mL/kg¶)	100	100 to 200
Na^+ (mEq/kg)	7 to 10	5 to 13
Cl^- (mEq/kg)	3 to 5	5 to 15
K^+ (mEq/kg)	3 to 5	4 to 6
PO_4 (mmol/kg)	5 to 7	3 to 7
Mg^{++} (mEq/kg)	1 to 2	1 to 2
Ca^{++} (mEq/kg)	1 to 2	1 to 2

Data are from Ennis et al (1994) and Kreisberg (1978).

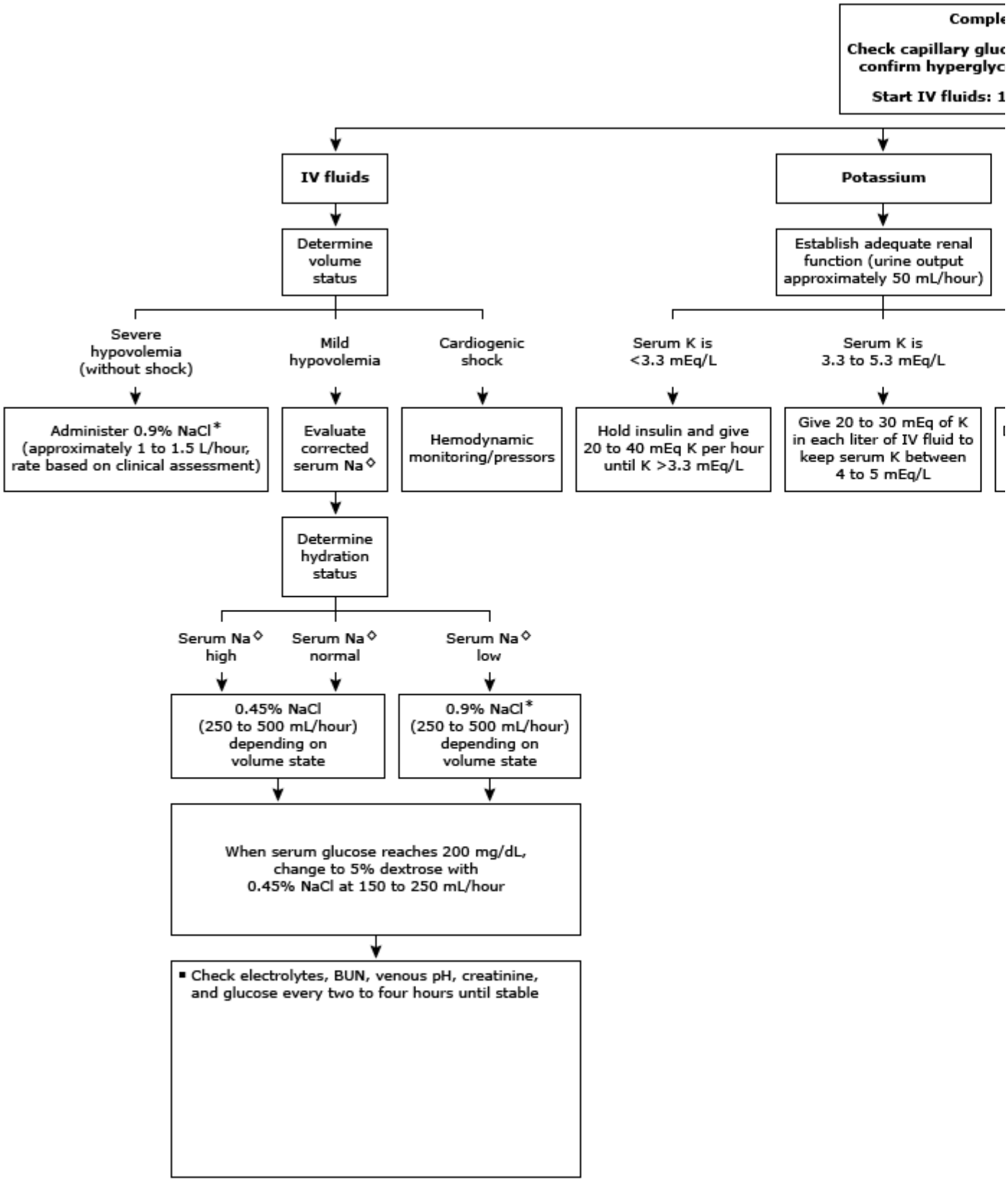
DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state; Na^+: sodium; Cl^-: chloride; K^+: potassium; PO_4: phosphate; Mg^{++}: magnesium; Ca^{++}: calcium.

* Fluid and electrolyte deficits vary widely depending on the severity of DKA or HHS. Adequacy of fluid replacement is judged by frequent hemodynamic and laboratory monitoring.

¶ Per kilogram of body weight.

Graphic 76060 Version 7.0

Treatment of diabetic ketoacidosis in adults



DKA diagnostic criteria: Serum glucose >250 mg/dL, arterial pH <7.3, serum bicarbonate <18 mEq/L, and at least moderate ketonuria or ketonemia. Normal laboratory values vary; check local lab normal ranges

for all electrolytes.

BUN: blood urea nitrogen; DKA: diabetic ketoacidosis; H_2O: water; HCO_3: bicarbonate; IV: intravenous; K: potassium; KCl: potassium chloride; Na: sodium; NaCl: sodium chloride; $NaHCO_3$: sodium bicarbonate; SC: subcutaneous.

* Isotonic buffered crystalloid (eg, Lactated Ringer) is a reasonable alternative.

¶ After history and physical examination, obtain capillary glucose and serum or urine ketones. Begin 1 L of 0.9% NaCl (or buffered crystalloid) over 1 hour, and draw arterial blood gas (or mixed venous blood gas), complete blood count with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram and, if needed, chest radiograph and specimens for bacterial cultures.

Δ If initial serum K is <3.3 mEq/L, hold insulin and give KCl until K is >3.3 mEq/L.

◇ Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2 mEq to sodium value for corrected serum sodium value).

§ 100 mmol $NaHCO_3$ = 100 mEq $NaHCO_3$.

¥ An alternative IV insulin regimen is to give a continuous IV infusion of regular insulin at 0.14 units/kg/hour; at this dose, an initial IV bolus is not necessary.

‡ Please refer to the UpToDate topic on DKA for the definition of DKA resolution.

† This is an UpToDate clinical suggestion.

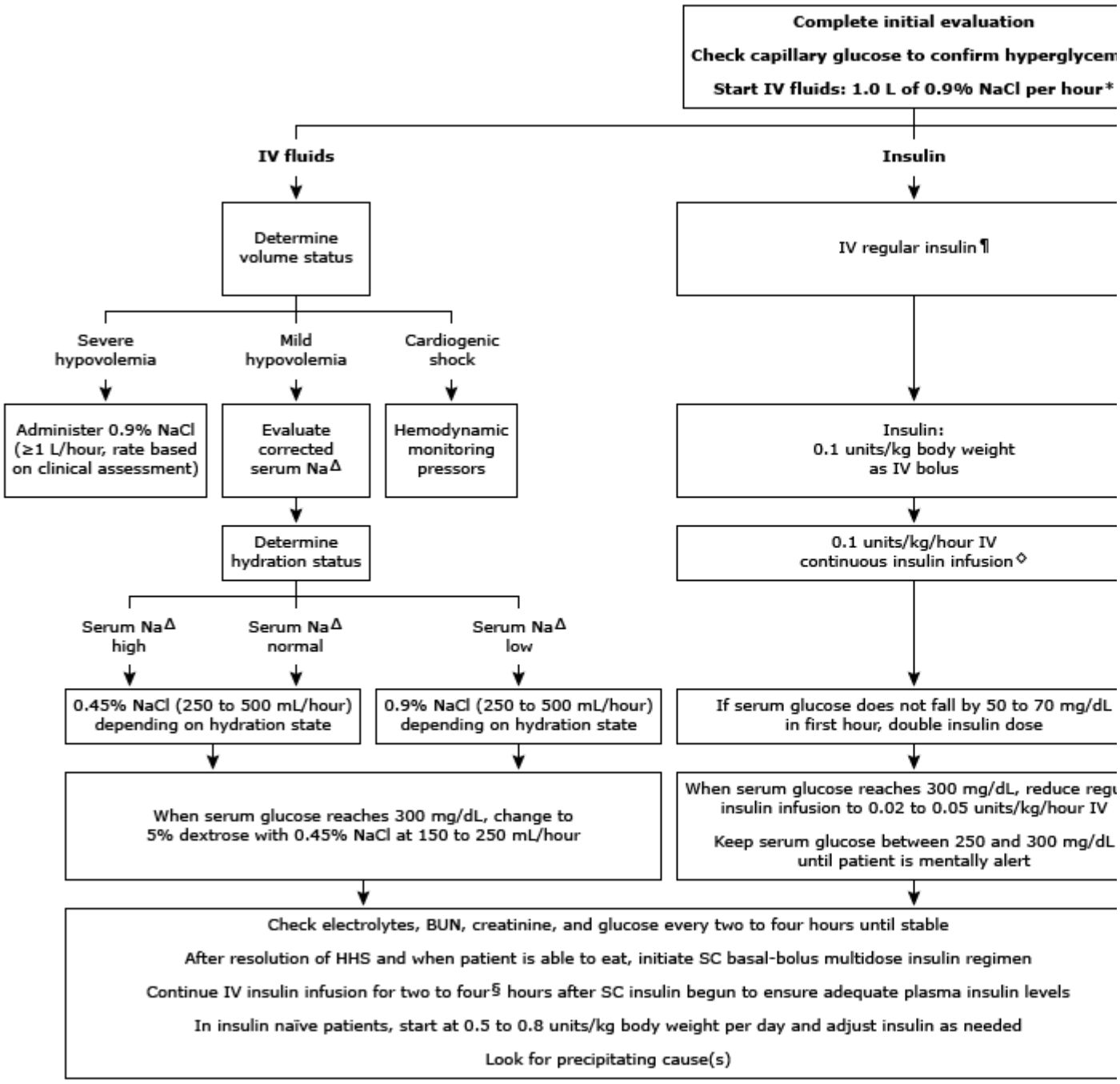
Adapted from: Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29:2739.

Updated with additional information from:

1. *Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335.*
2. *Umpierrez GE, Cuervo R, Karabell A, et al. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care 2004; 27:1873.*

Graphic 61747 Version 15.0

Treatment of hyperosmolar hyperglycemic state in adults



HHS diagnostic criteria: Serum glucose >600 mg/dL, arterial pH >7.3, serum bicarbonate >15 mEq/L, and minimal ketonuria and ketonemia. Normal laboratory values vary; check local lab normal ranges for all electrolytes.

HHS: hyperosmolar hyperglycemic state; IV: intravenous; NaCl: sodium chloride; K: potassium; Na: sodium; BUN: blood urea nitrogen; SC: subcutaneous.

* After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin 1 liter of 0.9% NaCl over one hour, and draw arterial blood gases, complete blood count

with differential, urinalysis, serum glucose, BUN, electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest radiograph, and specimens for bacterial cultures, as needed.

¶ If initial serum K is < 3.3 mEq/L, hold insulin and give potassium chloride until K is >3.3 mEq/L.

Δ Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dL glucose >100 mg/dL, add 2.0 mEq to sodium value for corrected serum sodium value).

◇ An alternative IV insulin regimen is to give a continuous intravenous infusion of regular insulin at 0.14 units/kg per hour; at this dose, an initial intravenous bolus is not necessary.

§ This is an UpToDate clinical suggestion.

Adapted and updated with additional information from:

1. *Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335.*

Graphic 67368 Version 8.0

Diabetic ketoacidosis in adults: Rapid overview of emergency management

Clinical features
DKA usually evolves rapidly over a 24-hour period.
The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. Common, early signs of ketoacidosis include nausea, vomiting, abdominal pain, and hyperventilation.
As hyperglycemia worsens, neurologic symptoms appear and may progress to include lethargy, focal deficits, obtundation, seizure, and coma.
Common causes of DKA include: infection; noncompliance, inappropriate adjustment, or cessation of insulin; new-onset diabetes mellitus; and myocardial ischemia.
Evaluation and laboratory findings
Assess vital signs, cardiorespiratory status, and mental status.
Assess volume status: vital signs, skin turgor, mucosa, urine output.
Obtain the following studies: serum glucose, urinalysis and urine ketones, serum electrolytes, BUN and creatinine, plasma osmolality, mixed venous blood gas, electrocardiogram; add serum ketones if urine ketones present.
DKA is characterized by hyperglycemia, an elevated anion gap* metabolic acidosis, and ketonemia. Dehydration and potassium deficits are often severe.
Serum glucose is usually greater than 250 mg/dL (13.9 mmol/L) and less than 800 mg/dL (44.4 mmol/L) In certain instances (eg, insulin given prior to emergency department arrival), the glucose may be only mildly elevated.
Additional testing is obtained based on clinical circumstances and may include: blood or urine cultures, lipase, chest radiograph.
Management
Stabilize the patient's airway, breathing, and circulation.
Obtain large bore IV (≥16 gauge) access; monitor using a cardiac monitor, capnography, and pulse oximetry.
Monitor serum glucose hourly, and basic electrolytes and venous pH or bicarbonate every two to four hours until the patient is stable.
Determine and treat any underlying cause of DKA (eg, pneumonia or urinary infection, myocardial ischemia).
Replete ECF volume and free water deficits:
▪ Give several liters of IV isotonic (0.9%) saline as rapidly as possible to patients with signs of shock

▪ Give IV isotonic (0.9%) saline at 15 to 20 mL/kg per hour (ie, 1 to 1.5 L per hour for an average-sized adult), in the absence of cardiac compromise, for the first few hours to hypovolemic patients without shock.
▪ After intravascular volume is restored, give one-half isotonic (0.45%) saline at 4 to 14 mL/kg per hour if the corrected serum Na+[¶] is normal or elevated; isotonic saline is continued if the corrected serum Na+[¶] is reduced.
▪ Add dextrose to the saline solution when the serum glucose reaches ~200 mg/dL (11.1 mmol/L).
Replete potassium (K+) deficits:
▪ Regardless of the initial measured serum K+, patients with DKA have a large total body K+ deficit.
▪ Manage replacement based on initial serum K+ value:
• <3.3 mEq/L – Hold insulin and give potassium chloride 20 to 40 mEq/hour IV until K+ concentration is above 3.3 mEq/L; rarely, additional potassium supplementation may be necessary to avoid life-threatening muscle weakness and cardiac arrhythmias.
• 3.3 to 5.3 mEq/L – Give potassium chloride 20 to 30 mEq per liter IV fluid; maintain serum K+ between 4 to 5 mEq/L.
• >5.3 mEq/L – Do not give potassium; check serum K+ every 2 hours; delay administration of potassium chloride until serum K+ has fallen to 5 to 5.2 mEq/L.
Give insulin:
▪ For patients with K+ <3.3 mEq/L, do **not** give insulin; replete K+ and fluid deficit first.
▪ For patients with K+ ≥3.3 mEq/L, give regular insulin. Either of 2 regimens can be used: 0.1 units/kg IV bolus, then start a continuous IV infusion 0.1 units/kg per hour; **or** do not give bolus and start a continuous IV infusion at a rate of 0.14 units/kg per hour.
▪ If serum glucose does not fall by at least 50 to 70 mg/dL (2.8 to 3.9 mmol/L) in the first hour, double the rate of insulin infusion.
▪ When the serum glucose reaches 200 mg/dL (11.1 mmol/L), it may be possible to decrease the infusion rate to 0.02 to 0.05 units/kg per hour.
▪ Continue insulin infusion until ketoacidosis is resolved, serum glucose is below 200 mg/dL (11.1 mmol/L), and subcutaneous insulin is begun.
Give sodium bicarbonate to patients with pH below 6.90:
▪ If the arterial pH is below 6.90, give 100 mEq of sodium bicarbonate plus 20 mEq of potassium chloride in 400 mL sterile water over two hours; may be repeated if venous pH remains below 7.00.

DKA: diabetic ketoacidosis; BUN: blood urea nitrogen; IV: intravenous; ECF: extracellular fluid; Na: sodium; K: potassium.

* Patients with DKA usually present with a serum anion gap greater than 20 mEq/L (normal range approximately 3 to 10 mEq/L). However, the increase in anion gap is variable, being determined by several factors: the rate and duration of ketoacid production, the rate of metabolism of the ketoacids and their loss in the urine, and the volume of distribution of the ketoacid anions.

¶ Serum Na+ should be corrected for hyperglycemia; for each 100 mg/dL serum glucose exceeds 100 mg/dL (5.5 mmol/L), add 2 mEq to plasma Na+ for correction of Na+ value for hyperglycemia. A calculator to determine serum Na+ corrected for hyperglycemia is available separately in UpToDate.

Graphic 57723 Version 5.0

Patient data flow sheet

Patient name: _____ Date: _____

Hour											
Mental status*											
Vital signs											
Temperature											
Pulse											
Respiration (rate and depth)¶											
Blood pressure											
Chemistries											
Serum glucose											
Serum ketones											
Urine ketones											
Serum Na^+ (mEq/L)											
Serum K^+ (mEq/L)											
Serum Cl^- (mEq/L)											
Serum HCO_3^- (mEq/L)											
Serum BUN (mg/dL)											
Effective osmolality$^\Delta$											
Anion gap											
Blood gases											
pH (specify venous [V] or arterial [A])											
pO_2											
pCO_2											
O_2 saturation											
Insulin (units in past hour)											
Route											
Intravenous											
Subcutaneous											
Intramuscular											
Fluid/metabolites (past hour)											
0.45% NaCl (mL)											
0.9% NaCl (mL)											
5% dextrose (mL)											
Other											
Output											
Urine (mL)											
Other											

Na^+: sodium; K^+: potassium; Cl^-: chloride; HCO_3^-: bicarbonate; BUN: blood urea nitrogen; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide; O_2: oxygen; NaCl: sodium chloride.

* A: alert; D: drowsy; S: stuporous; C: comatose.

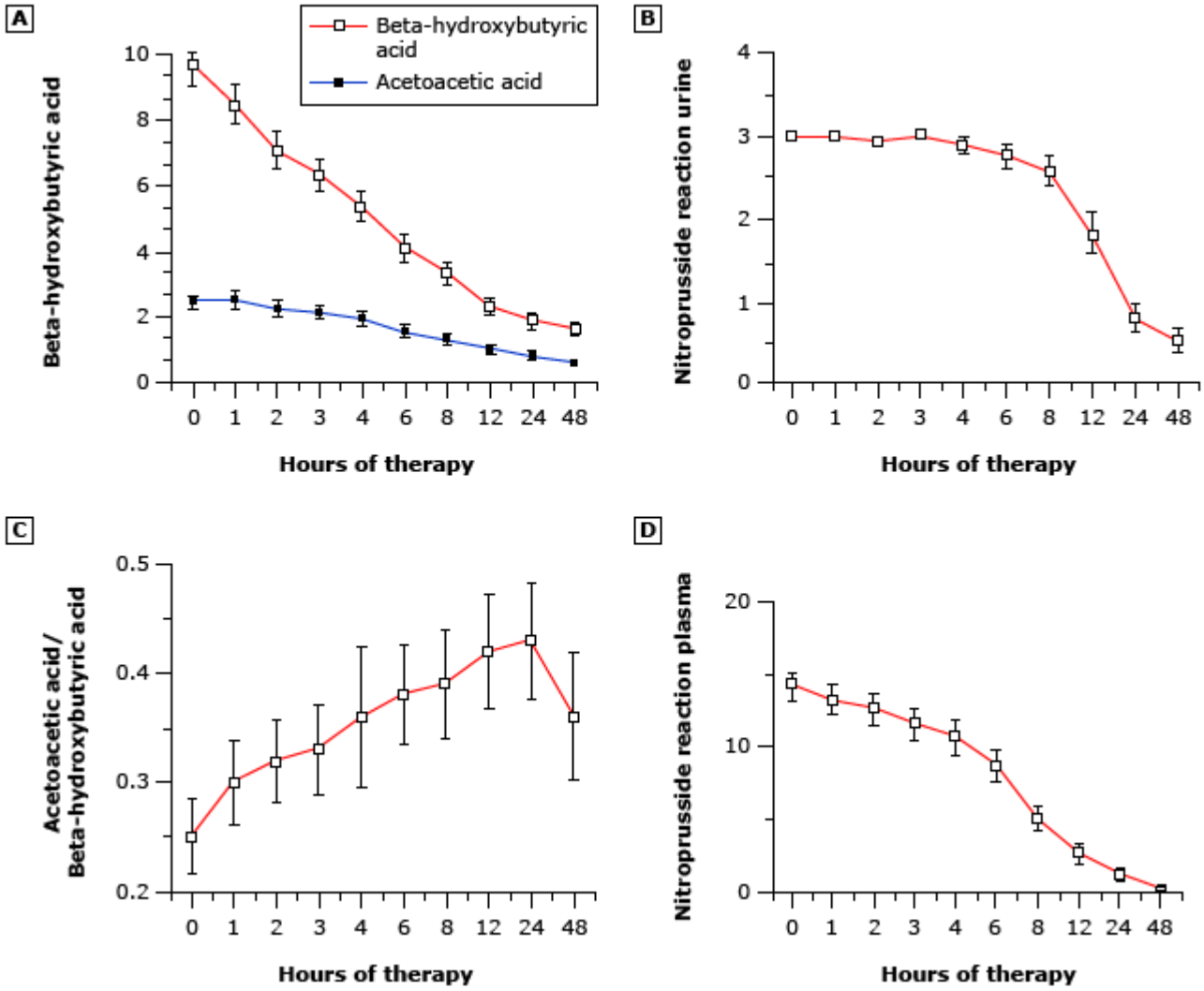
¶ D: deep; S: shallow; N: normal.

Δ [2 × Na (mEq/L)] + [glucose (mg/dL) ÷ 18].

Adapted from: Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In: Joslin's Diabetes mellitus, 13th ed, Kahn CR, Weir GC (Eds), Lea and Febiger 1994.

Graphic 62913 Version 3.0

Ketone response to treatment of diabetic ketoacidosis



Comparative data in 37 patients with diabetic ketoacidosis with regard to plasma acetoacetic acid and beta-hydroxybutyric acid (A); ratio of acetoacetic acid to beta-hydroxybutyric acid (C); and ketone bodies (nitroprusside reaction) in the urine (B) and plasma (D) before and during low-dose intravenous infusion of insulin for 48 hours.

Graphic 60366 Version 11.0