Chapter 2
Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome

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Précis

1. Clinical setting—Any altered state of well being in the context of significant hyperglycemia in a patient with type 1 (DKA) or advanced type 2 diabetes mellitus (DKA or HHS), particularly during acute illness, may signify one of these diabetic emergencies.

2. Diagnosis

(a) History: Most patients with diabetic ketoacidosis (DKA) or with hyperosmolar hyperglycemic state (HHS) will have a history of diabetes, and a history of altered insulin dose, infection, significant medical “stress”. Antecedent symptoms of polyuria and polydipsia, lassitude, blurred vision, and mental status changes may predominate the clinical picture. With DKA, abdominal pain and tachypnea are often present.

(b) Physical examination usually reveals an altered sensorium, signs of volume contraction/dehydration (tachycardia, hypotension, dry mucus membranes, “tenting” of the skin); in DKA, the odor of acetone in the breath.

(c) Laboratory evaluation. The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH < 7.30, serum bicarbonate < 15 mEq/l
and moderate degree of ketonemia and/or ketonuria. Patients with HHS present with extreme hyperglycemia (blood glucose > 600 mg/dL), increased osmolality (> 320 mOsm/kg) and profound dehydration/volume contraction. The laboratory evaluation of a patient with hyperglycemic emergency should include measurement of blood glucose and hemoglobin A1c, arterial blood gases, serum electrolytes, ketones and osmolality, renal function and urinalysis. A work-up for sepsis or other precipitating causes should be initiated if indicated.

3. Treatment

(a) DKA

1. Fluid: Estimated fluid deficit is 5–7 liters. Correct with normal saline, 2L in the first 2 hours, the remainder over the next 22 hours.
2. Insulin: IV bolus of 0.1 U/Kg regular insulin followed by an intravenous infusion of 0.1 U/kg/h. Goal is to reduce plasma glucose by 50–75 mg/dL/h. Initial target plasma glucose is 200–250 mg/dL. Once achieved, reduce insulin rate and provide dextrose to ‘clamp’ the plasma glucose until acidosis/anion gap resolved.
3. Acid/base – pH will climb with plasma expansion and insulin administration. Use small amounts of sodium bicarbonate only for severe acidemia (pH <6.9).
4. Electrolytes: Close monitoring and correction of serum potassium is critical. (If serum potassium <3.5, correct hypokalemia before any insulin is given.)
5. Search for cause: Seek to determine underlying precipitant, such as treatment non-adherence, infection, myocardial infarction, etc.

(b) HHS

1. Fluid: Estimated fluid deficits typically larger than in DKA (7–9 liters). Correction/maintenance of plasma volume with normal saline is critical in older patients. Correct rate depends on blood pressure, other signs of volume contraction and any history of underlying cardiovascular disease, especially heart failure.
2. Insulin: Should be initiated after initial saline plasma expansion. IV bolus of 0.1 U/Kg regular insulin followed by an intravenous infusion of 0.1 U/kg/h. Goal is to reduce plasma glucose by 50–75 mg/dL/h. Target plasma glucose is 250–300 mg/dL.
3. Acid/base- By definition, no major deficits related to HHS itself.
4. Electrolytes: Derangements not as common as in DKA, but monitoring is still required.
5. Search for cause: As above.
Introduction

Diabetic Ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS) are two acute and life-threatening complications of diabetes requiring prompt recognition and aggressive therapy to optimize clinical outcomes. Although they share certain features, DKA and HHS differ clinically according to the degree of hyperglycemia and the presence of ketoacidosis. The fundamental difference between the two conditions is that a small residual amount of insulin prevents significant ketosis and acidosis in HHS. Descriptive definitions of DKA and HHS and the criteria for classification of the severity of the former are shown in Table 2.1.

Patients with DKA present with hyperglycemia, ketonemia, and metabolic acidosis secondary to absolute or profound relative insulin deficiency. HHS is characterized by a greater severity of plasma glucose elevation, marked increase of plasma osmolality, absent to mild ketosis, and altered mental status. In HHS, residual secretion minimizes ketone body production but is not able to control hyperglycemia. The older terms “hyperglycemic hyperosmolar nonketotic coma” and “hyperglycemic hyperosmolar nonketotic state” have been replaced with the term “hyperglycemic hyperosmolar syndrome (or state)” to reflect the fact that different levels of mentation and ketosis may indeed be present.

Most patients with DKA have type 1 diabetes, which is associated with absolute insulin deficiency. Patients with advanced or severe type 2 diabetes can also be at risk during acute illnesses. HHS occurs almost exclusively in type 2 diabetes patients, who continue to demonstrate some degree of insulin secretion.

Table 2.1 Diagnostic criteria for diabetic ketoacidosis (DKA) and hyperosmolar state (HHS) (Adapted from Kitabchi et al., Diabetes Care, 2001 [1])

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>HHS</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7.00–7.24</td>
<td>&lt;7.00</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15–18</td>
<td>10 to &lt;15</td>
<td>&lt;10</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Urine ketonesa</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>None — small</td>
</tr>
<tr>
<td>Serum ketonesa</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>None — small</td>
</tr>
<tr>
<td>Effective serum</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>osmolality (mOsm/kg water)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gapc</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>Variable, but usually normal</td>
</tr>
<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
</tbody>
</table>

a Nitroprusside reaction method
b Calculation: 2 [measured Na (mEq/L)] + glucose (mg/dL)/18
c Calculation: Na⁺ − (Cl⁻ + HCO⁻₃), in mEq/L
The events leading to DKA and HHS are shown in Fig. 2.1. In DKA, absent or severely reduced insulin concentrations, increased insulin-counterregulatory hormones (cortisol, glucagon, growth hormone, and catecholamines), and peripheral insulin resistance result in hyperglycemia and ketosis. Hyperglycemia evolves through decreased glucose utilization by peripheral tissues and accelerated hepatic gluconeogenesis and glycogenolysis [1–4]. Due to increased lipolysis and decreased lipogenesis, abundant circulating free fatty acids are converted to ketone bodies (beta-hydroxybutyrate, acetoacetate, and acetone) by the liver. Beta-hydroxybutyrate and acetoacetate are two relatively strong acids. At physiological pH, these two ketoacids dissociate completely and the excess hydrogen ions bind bicarbonate, resulting in decreased serum [HCO\(_3\)^−] concentrations. Ketones thus circulate in the anionic form, leading to the development of the anion gap metabolic acidosis that characterizes DKA. Hyperglycemia-induced osmotic diuresis also leads to dehydration, hyperosmolality, electrolyte losses, and subsequent decreased plasma volume and glomerular filtration. With decline in renal function, glycosuria and ketonuria

Fig. 2.1 Schematic overview of the pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome (Adapted from Kitabchi et al., Diabetes Care, 2001 [1]). DKA diabetic ketoacidosis, FFA free fatty acids, HHS hyperosmolar hyperglycemic syndrome

Pathogenesis

The events leading to DKA and HHS are shown in Fig. 2.1. In DKA, absent or severely reduced insulin concentrations, increased insulin-counterregulatory hormones (cortisol, glucagon, growth hormone, and catecholamines), and peripheral insulin resistance result in hyperglycemia and ketosis. Hyperglycemia evolves through decreased glucose utilization by peripheral tissues and accelerated hepatic gluconeogenesis and glycogenolysis [1–4]. Due to increased lipolysis and decreased lipogenesis, abundant circulating free fatty acids are converted to ketone bodies (beta-hydroxybutyrate, acetoacetate, and acetone) by the liver. Beta-hydroxybutyrate and acetoacetate are two relatively strong acids. At physiological pH, these two ketoacids dissociate completely and the excess hydrogen ions bind bicarbonate, resulting in decreased serum [HCO\(_3\)^−] concentrations. Ketones thus circulate in the anionic form, leading to the development of the anion gap metabolic acidosis that characterizes DKA. Hyperglycemia-induced osmotic diuresis also leads to dehydration, hyperosmolality, electrolyte losses, and subsequent decreased plasma volume and glomerular filtration. With decline in renal function, glycosuria and ketonuria
are attenuated, further exacerbating hyperglycemia, hyperosmolality, and ketoacidosis. Activation of the sympathoadrenal system further counteracts insulin action, heightening all of these features.

HHS is also caused by a reduction in the net effective action of circulating insulin and an increase in counterregulatory hormones, leading to hyperglycemia and hyperosmolality. The key difference between HHS and DKA is that insulin levels in HHS are inadequate to control hyperglycemia, but generally sufficient to prevent significant ketosis, and as a result, acidosis.

Recent studies have shown that patients in hyperglycemic crisis also exhibit a severe pro-inflammatory state characterized by elevated cytokine (tumor necrosis factor-α (alpha), interleukin-β (beta), −6 and −8), C-reactive protein, reactive oxygen species, lipid peroxidation, and plasminogen activator inhibitor-1 [5].

New-onset type 1 diabetes (and, in some circumstances, type 2) can present with DKA. The most common precipitating factors are omission of insulin or inadequate insulin coverage especially during some other acute illness (e.g., gastroenteritis, influenza), severe infections, myocardial infarction, stroke, pancreatitis, or major surgery. Insulin pump malfunction, psychiatric illness, eating disorders, and drug abuse can also be associated with DKA. Administration of medications such as corticosteroids, conventional and atypical antipsychotic drugs, thiazide diuretics, and beta blockers has also been reported to promote the development of DKA.

HHS is seen exclusively in type 2 diabetes and can sometimes be its initial presentation. Infection is the major precipitating factor (pneumonia, pyelonephritis, etc.) occurring in about 50 % of the patients. Other acute illnesses such as myocardial infarction and stroke, which cause the release of counterregulatory hormones, and intra-abdominal processes, including acute pancreatitis can be the stimulus for HHS. Medications associated with DKA also have been associated with HHS. Nonetheless, in about 20 % of patients presenting with hyperglycemic crisis there is no obvious cause—likely due to an abrupt increased insulin requirement for some unidentifiable reason, with superimposed effects of gluco-toxicity, which describes the phenomenon of worsening beta-cell secretion of insulin caused by hyperglycemia itself.

**Diagnosis**

**History and Physical Examination**

DKA and HHS are medical emergencies that require urgent recognition and treatment. The initial approach to these patients should include a rapid but thorough history and physical examination with special focus on patency of airways, mental status, state of hydration, cardiovascular and renal integrity, and potential sources of infection.
The development of DKA is usually relatively acute, occurring in less than 24–48 h, whereas HHS usually evolves over several days to weeks. The typical symptoms of unrestrained hyperglycemia in both syndromes include polyuria, polydipsia, blurred vision, fatigue, weakness, and weight loss. DKA patients usually present with vomiting and abdominal pain probably due to delayed gastric emptying and ileus caused by electrolyte abnormalities and/or acidosis. Physical findings include poor skin turgor, tachycardia, and hypotension. In DKA, there may be a fruity odor to the breath (from ketosis) as well as rapid, regular, and deep respirations (Kussmaul breathing), the latter representing an effort to mitigate the impact of metabolic acidosis by inducing a compensatory respiratory alkalosis. Patients with HHS can present with focal neurological signs (hemiparesis, hemianopsia) and seizures. Mental status can vary from alertness to lethargy and coma. Serum osmolality is the most important determinant of mental status in HHS. In particular, obtundation and coma may be seen when the effective osmolality exceeds 330 mOsm/kg [6].

Even though infection is a common precipitating factor for hyperglycemic crises, the body temperature can be misleadingly normal or low due to peripheral vasodilation.

**Laboratory Findings**

The easiest and most urgent laboratory tests are determination of blood glucose by finger stick and urinalysis with reagent strips for ketones and glucose allowing for the detection or at least the strong suspicion of these hyperglycemic crises before the patient is seen. These can be done by the patient at home.

<table>
<thead>
<tr>
<th>Metabolic evaluation</th>
<th>Infectious disease evaluation</th>
<th>Othersa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>CBC with differential</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Chest X-ray</td>
<td>Urine toxicology panel</td>
</tr>
<tr>
<td>Electrolytes (monovalent and divalent: Na⁺, K⁺, Cl⁻, HCO₃⁻, Ca²⁺, PO₄³⁻, Mg²⁺)</td>
<td>Urine culture</td>
<td>Pregnancy test</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Blood cultures</td>
<td></td>
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<tr>
<td>Blood urea nitrogen (BUN) and creatinine</td>
<td>Viral nasal swab</td>
<td></td>
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<tr>
<td>Arterial blood gases (ABG)</td>
<td></td>
<td></td>
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<tr>
<td>Liver function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase and lipase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aIf clinically indicated
The initial laboratory evaluation of a patient with DKA or HHS should include measurement of blood glucose, arterial blood gases, renal function, serum electrolytes, ketones, serum osmolality, complete blood count with differential, and urinalysis. A work-up for sepsis should be initiated by obtaining blood and urine cultures and a chest X-ray if clinically indicated. Additional tests include EKG and determination of hemoglobin A1c level, the latter to assess for chronicity and degree of hyperglycemia (Table 2.2).

The diagnostic criteria for DKA include blood glucose above 250 mg/dL, arterial pH <7.30, serum bicarbonate <15 mEq/L, and moderate degree of ketonemia and/or ketonuria (Table 2.1) [1]. Hyperglycemia is a key diagnostic criteria of DKA; however, 10% of DKA patients will have a glucose level below 250 mg/dL [7], sometime due to insulin administration before getting to the hospital decreased nutritional intake and decreased gluconeogenesis due to recent ethanol consumption or advanced liver disease [8, 9].

Accumulation of ketones results in an anion gap metabolic acidosis. The anion gap is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium). In the older literature, a level above 14–15 mEq/L was thought to be consistent with an increased anion gap metabolic acidosis. However, most laboratories currently measure sodium and chloride using ion-specific electrodes. Plasma chloride level measured by this method is usually 2–6 mEq/L higher than with prior analytical methods. Therefore, using the ion-specific technique, an anion gap of >10–12 mEq/L would suggest the presence of an anion gap acidosis [10, 11]. Arterial blood gases support the diagnosis with the presence of acidemia.

The key laboratory features of DKA are ketonemia and ketonuria. The ratio between the two main ketoacids, beta-hydroxybutyrate and acetoacetate, depends on the prevailing redox state. In high redox states, such as DKA (as well as lactic acidosis), beta-hydroxybutyrate predominates. Assessment of ketone status is usually performed with the nitroprusside reaction, which provides a semiquantitative measurement of acetoacetate and acetone. However, the nitroprusside reaction does not detect beta-hydroxybutyrate, thus underestimating the severity of ketoacidosis. If available, direct measurement of serum beta-hydroxybutyrate can be helpful in establishing the diagnosis.

Patients with HHS present with extreme hyperglycemia (blood glucose >600 mg/dL), increased osmolality (>320 mOsm/kg), and profound dehydration/volume contraction. The effective serum osmolality is calculated as follows: 2 [measured Na (mEq/L)] + glucose (mg/dL)/18, with normal value being 290±5 mOsm/kg (blood urea nitrogen, which enters the equation for total serum osmolality, is not included here as it is freely diffusible across cell membranes and is therefore not considered an “effective osmole”). Usually in HHS, the anion gap is normal and serum bicarbonate level is over 20 mEq/L. However, some patients can present with mild acidosis, due to the accumulation of ketone bodies in low concentration and/or lactate resulting from generalized hypoperfusion.
Both DKA and HHS are associated with large fluid and electrolyte deficits (Table 2.3). The development of dehydration and electrolyte depletion is the result of hyperglycemia, insulin deficiency and, in DKA, keto-anion excretion.

Hyperglycemia causes an osmotic diuresis. During severe hyperglycemia the renal threshold of glucose and ketones is exceeded. The osmotic effect of glucosuria results in impaired water and sodium chloride reabsorption in the proximal tubule and loop of Henle [12]. Insulin deficiency itself may further contribute to fluid and electrolyte losses because insulin stimulates salt and water resorption in the proximal and distal nephron and phosphate reabsorption in the proximal tubule. Ketoacid excretion exacerbates solute diuresis by causing urinary cation excretion in the form of sodium, potassium, and ammonium salts.

The severity of dehydration is greater in HHS than in DKA likely due to more gradual and longer duration of metabolic decompensation and decreased fluid intake. Also, nausea and vomiting (in DKA) and fever, when present, can further contribute to dehydration.

Serum sodium concentration is markedly decreased because of intracellular water shifting to the extracellular compartment in order to equilibrate hyperosmolality. Usually the admission sodium is factitiously low because of the hyperglycemia and hyperlipidemia. The corrected sodium can be calculated by adding 1.6 mEq to the reported sodium value for every 100 mg of glucose over 100 mg/dL. As a result, a normal or high-measured serum sodium in this setting actually indicates severe state of dehydration, as is often the case in patients presenting with HHS.

The patient’s serum potassium may be initially elevated due to an extracellular shift of potassium caused by insulin deficiency, acidemia, and hypertonicity, which is falsely reassuring as the total body potassium stores are probably depleted. A low or low-normal potassium level suggests severe total body potassium depletion.

Patients with uncontrolled hyperglycemia are usually in a negative phosphate balance because of phosphaturia caused by osmotic diuresis and the shift of phosphate out of the cell in the setting of acidosis.

### Table 2.3  Typical deficits of water and electrolytes in DKA and HHS (Adapted from Kitabchi et al., Diabetes Care, 2006 [29])

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total water (L)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Water (mL/kg)(^a)</td>
<td>100</td>
<td>100–200</td>
</tr>
<tr>
<td>Na(^+) (mEq/kg)</td>
<td>7–10</td>
<td>5–13</td>
</tr>
<tr>
<td>Cl(^−) (mEq/kg)</td>
<td>3–5</td>
<td>5–15</td>
</tr>
<tr>
<td>K(^+) (mEq/kg)</td>
<td>3–5</td>
<td>4–6</td>
</tr>
<tr>
<td>PO(_4^{3−}) (mmol/kg)</td>
<td>5–7</td>
<td>3–7</td>
</tr>
<tr>
<td>Mg(^{2+}) (mEq/kg)</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Ca(^{2+}) (mEq/kg)</td>
<td>1–2</td>
<td>1–2</td>
</tr>
</tbody>
</table>

\(^a\)Per kilogram of body weight
Leukocytosis around 10,000–15,000 mm$^3$ is a common finding in DKA and may not be the result of an infection. This is attributed to stress and elevation in stress hormones. However, leukocytosis above 25,000 mm$^3$ suggests a septic process and should trigger further evaluation.

Hyperamylasemia has been reported in patients with DKA. It is not always being associated with pancreatitis. The origin of amylase in DKA is usually a non-pancreatic tissue such as the salivary glands. Measuring a lipase level can be useful in the differential diagnosis; however, lipase also can be elevated in the absence of pancreatitis [13]. The mechanisms of increased amylase and lipase levels in DKA are not well defined.

Moderate hypertriglyceridemia is common during episodes of DKA [14]. The deficiency of insulin activates lipolysis in adipose tissue releasing increased free fatty acids, which accelerates the formation of very low density lipoprotein (VLDL) in the liver. In addition, reduced activity of lipoprotein lipase in peripheral tissue decreases the removal of VLDL from the plasma, resulting in hypertriglyceridemia. Severe hypertriglyceridemia and hypertriglyceridemia-induced pancreatitis leading to DKA or HHS are well recognized [15]. Severe hypertriglyceridemia may spuriously lower serum glucose (pseudonormoglycemia) [16] and serum sodium (pseudohyponatremia) [17] in laboratories using volumetric testing and dilution samples with ion-specific electrodes.

**Differential Diagnosis**

DKA must be differentiated from other conditions that present with ketoacidosis and anion gap metabolic acidosis. Starvation and alcoholic ketoacidosis are not typically associated with hyperglycemia above 200 mg/dL and, usually, the bicarbonate level is greater than 18 mEq/L. Other causes of an anion gap metabolic acidosis include lactic acidosis, acute renal failure, and the ingestion of methanol, ethylene glycol, paraldehyde, and salicylate. The origin of the anion gap can usually be ascertained by assessing the ketone concentrations in the plasma. HHS is difficult to confuse with other conditions, given its narrowly defined diagnostic criteria. Overlap syndromes with features of both DKA and HHS, however, can be encountered in clinical practice. These may occur in patients with a slower development of ketoacidosis and, as a result, more protracted urinary losses of free water, resulting in hyperosmolality.

**Treatment**

The therapeutic goals of DKA and HHS management include restoration of volume status, correction of hyperglycemia and ketoacidosis (in DKA), correction of electrolyte abnormalities, treatment of precipitating factors, and prevention of the
complications of DKA and HHS. Adequate intravenous (IV) access is essential with two larger bore IV peripheral lines or a central line. A suggested protocol for the management of patients with DKA and HHS is summarized in Fig. 2.2.

**Fluid Therapy**

In the emergency room, fluid resuscitation is critical for intravascular, interstitial, and intracellular volume and restoration of renal perfusion. The average fluid loss is approximately 5–7 L in DKA and 7–9 L in HHS (Table 2.3). The IV fluid administration replaces the fluid and electrolyte deficiencies, while simultaneously reducing plasma glucose concentrations and counterregulatory hormones, partially through dilution but also through volume expansion and resultant expansion of plasma volume. IV fluids should be administered before starting insulin in HHS, especially in older patients with tenuous cardiovascular status, in order to preserve vascular volume (see below).
Normal saline is generally given in the first hour at a rate of 15–20 mL/kg body weight/h or 1–1.5 L in the first hour, although care is required in older patients with underlying cardiovascular disease. After initial stabilization, if the corrected serum sodium is normal or elevated, normal saline can be changed to half-normal saline at a rate of ~250–500 mL/h. If the corrected sodium is low, normal saline can be continued at a similar rate. Fluid replacement should correct the estimated deficit in the first 24 h, with 50 % of fluid resuscitation in the first 8–12 h. In patients with HHS, the change in serum osmolality should not exceed 3 mOsm/kg water/h.

The response to fluid resuscitation is judged by monitoring hemodynamic parameters (blood pressure and heart rate), clinical exam, urinary output, and laboratory values. In patients with renal or cardiac compromise fluid resuscitation should be conducted with caution to avoid fluid overload.

Once the serum glucose is 200–250 mg/dL in DKA, the insulin infusion rate should be reduced to 1–2 U/h and 5 % dextrose should be added to the IV fluids (this is termed the “glucose-insulin clamp” by some authorities). This technique will prevent hypoglycemia but will allow continuation of insulin administration sufficient in amount to resolve the ketoacidosis in DKA (i.e., to close the anion gap). A proposed algorithm for clamping the serum glucose using dextrose-containing IV fluids and IV insulin is outlined in Table 2.4.

Due to concerns that lowering the serum glucose too fast in HHS might promote the development of cerebral edema, some authorities recommend adding 5 % dextrose to the IV fluids when the serum glucose is 250–300 mg/dL until the patient is mentally alert [18]. In the majority of HHS cases, serum osmolality and mental status are normalized by the time the hyperglycemia is corrected, thus the “glucose clamp” will not often be necessary. Indeed, a simple lowering of the insulin infusion rate without the addition of dextrose can be sufficient, even in cases where the mental status remains abnormal.

<table>
<thead>
<tr>
<th>Serum glucose</th>
<th>IV fluid</th>
<th>Insulin infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>200–250 mg/dL in DKA</td>
<td>Change to D$_5$O.45%NS 100–200 mL/h$^{ab}$</td>
<td>Reduce insulin drip to 1–2 U/h$^c$</td>
</tr>
<tr>
<td></td>
<td>100 mL/h</td>
<td>1 U/h</td>
</tr>
<tr>
<td></td>
<td>200 mL/h</td>
<td>2 U/h</td>
</tr>
<tr>
<td>If serum glucose increases</td>
<td>Do not reduce IV fluids</td>
<td>Minor increases in insulin infusion rate (~0.5–1 U/h)$^d$</td>
</tr>
<tr>
<td>If serum glucose decreases</td>
<td>Increase IV fluids</td>
<td>Do not decrease insulin infusion rate</td>
</tr>
</tbody>
</table>

$^a$Provides 5–10 g of carbohydrates per hour
$^b$Alternative is 0.02–0.05 U/kg/h
$^c$Give insulin IV 1 U/h for every 5 g of dextrose IV/h
$^d$Highly insulin resistant patients who require large amounts of IV insulin may need as much as 5–10 U of insulin/h. Accordingly, insulin dose adjustments may need to be more aggressive. The insulin dose can likely be reduced gradually as hyperglycemia improves

Table 2.4 Suggested algorithm for clamping the blood glucose using dextrose-containing IV fluids and IV insulin in DKA
Insulin Therapy

The only contraindication to insulin therapy is a current serum potassium below 3.5 mEq/L as insulin will worsen the hypokalemia by shifting the potassium into the cells.

The administration of continuous intravenous infusion of regular insulin is the preferred route as it has short half-life, it is easy to titrate, and has a rapid onset and short duration of action. The insulin dose is similar in DKA and HHS. However, as mentioned before, initial volume expansion with crystalloid is recommended (at least 1 L) in the more profoundly dehydrated and older HHS patients. This recommendation is to protect the plasma volume; once insulin is administered, the consequent fall in circulating glucose concentrations will lead to an intracellular shift of water from the plasma compartment which can result in a precipitous drop in systemic blood pressure. Insulin treatment usually starts with an IV bolus of 0.1 U/kg body weight followed by a 0.1 U/kg body weight/hour continuous infusion. The goal of insulin therapy is to decrease serum glucose by 50–75 mg/dL/h. Overly aggressive reduction of glucose may result in brain edema. A suggested algorithm for adjusting the IV insulin drip during DKA and HHS treatment can be found in Table 2.5. Glucose levels should be monitored every 1 h initially, and once stabilized, every 2–3 h.

Treatment of patient with mild to moderate DKA with subcutaneous rapid-acting analogs (lispro, aspart) every 1–2 h in non-intensive care unit has been shown to be effective in several studies [19, 20]; however, until these studies are confirmed outside the research setting, the vast majority of patients with DKA and HHS should be treated with intravenous regular insulin. Preferably, patients with these hyperglycemic emergencies should be managed in an intensive care setting, mainly due to the requirements to continuous patient monitoring, frequent blood testing and reporting, and rapid titration of therapy that may be required.

Potassium Replacement

Potassium replacement is critical in managing patients with DKA and HHS. Renal and gastrointestinal losses contribute to a marked potassium deficit in most patients. Despite the total body potassium deficit, the serum potassium concentration can be
normal or elevated at presentation due to the acidosis, the insulin deficiency, and
the hyperosmolality, all of which cause a potassium shift from the intracellular to
the extracellular space. Administration of insulin results in a significant shift of
potassium into the cells and a fall in the serum potassium level. To prevent hypoka-
olemia, potassium chloride is usually added to the IV fluids if the serum potassium is
below the upper level of normal for the particular lab (5.0–5.2 mEq/L) and there is
a good urinary output (>50 mL/h). Careful monitoring of the serum potassium is a
critical part in the management of all hyperglycemic emergencies. Ideally, the
serum potassium should be measured every 2–4 h (along with other electrolytes)
and maintained between 4 and 5 mEq/L. To avoid cardiac and respiratory complica-
tions, patients who are hypokalemic prior to the initiation of treatment should not
receive insulin until the potassium level is above 3.5–4.0 mEq/L. Such patients
should receive aggressive potassium replacement (20–30 mEq/h) until potassium
level is above 3.5–4.0 mEq/L (see Fig. 2.2 for details).

**Phosphate Replacement**

At presentation, serum phosphate is often normal or high in spite of whole-body
phosphate deficit due to movement of phosphate out of the cells. As with potas-
sium balance, phosphate concentration decreases with insulin therapy. However,
the fall in serum phosphate level during DKA treatment is usually self-limited,
asymptomatic, and does not require treatment. Prospective randomized trials of
patients with DKA failed to show any benefit associated with supplementation
[21] and phosphate replacement can have adverse effects such as hypocalcemia
and hypomagnesemia [22]. Thus, phosphate replacement is not routinely recom-
mended; however, it should be considered in patients at risk for cardiac dysfunc-
tion, hemolytic anemia, and respiratory depression or when the phosphate
concentration is below 1 mg/dL. When needed, potassium phosphate
20–30 mEq/L can be added to the replacement fluids. The rate of phosphate
replacement should not exceed 4.5 mmol/h [23]. Because of the risk of hypocal-
cemia, serum calcium and phosphate levels should be monitored during phos-
phate infusion. No studies are available on the use of phosphate in treatment of
HHS. Phosphate levels should be tested but less frequently than routine electro-
lytes, perhaps every 8–12 h.

**Bicarbonate Therapy**

Bicarbonate use in DKA remains controversial. Treatment with insulin inhibits
lipolysis and ketoacid production and promotes keto-anion metabolism. Because
protons are consumed during keto-anion metabolism, bicarbonate is regenerated
leading to partial correction of metabolic acidosis with insulin therapy and vol-
ume expansion alone. However, severe acidosis can lead to impaired cardiac
contractility, cerebral vasodilatation, and severe gastrointestinal complications.
A randomized trial of 21 DKA patients with an admission arterial pH between 6.9 and 7.1 showed no difference in morbidity and mortality with bicarbonate use [24]. Not surprisingly, there are no prospective randomized trials on the use of bicarbonate in DKA patients with an arterial pH less than 6.9. Potential side effects of bicarbonate therapy include hypokalemia, worsening intracellular aci-
dosis (as a result of increased carbon dioxide production), delayed keto-anion metabolism, and development of paradoxical central nervous system acidosis [25–27].

Nonetheless, because severe acidosis may result in significant adverse cardiovas-
cular effects, it is recommended that patients with pH values <6.9 should receive 100 mmol of sodium bicarbonate (2 ampules) in 400 mL sterile water with 20 mEq potassium chloride at a rate of 200 mL/h for 2 h until the pH is >7. If the pH is still <7, the bicarbonate infusion can be repeated every 2 h until the pH is >7. Hypokalemia, if present, must be corrected before any bicarbonate administration. Profound acidosis can require a continuous bicarbonate infusion.

Search for Precipitating Factors

Infection is a major precipitating factor for hyperglycemic emergencies. Hence, it is important to search for underlying infections. If indicated, chest X-ray and blood and tissue cultures should be obtained. Appropriate antibiotic treatment should be initiated if a bacterial infection is identified.

Resolution of DKA and HHS

Criteria for resolution of DKA includes a serum glucose <200 mg/dL and two out of the following criteria: serum bicarbonate ≥15 mEq/L, a venous pH >7.3, and a calculated anion gap ≤12 mEq/L. Resolution of HHS includes normal serum osmo-
lality (<315 mOsm/kg), and normal mental status [18]. Please note that the serum bicarbonate may still be low even after DKA resolution due to an “expansion” non-
gap acidosis associated with aggressive IV crystalloid repletion. Thus, the anion gap is the best indicator of DKA resolution.

Transition to Subcutaneous Insulin

If the DKA or HHS has resolved but the patient is to remain NPO, IV insulin and fluid replacement should be continued. However, if the patient is able to eat, sub-
cutaneous insulin can be started, although this may be most conveniently done in conjunction with the patient’s next planned meal. As the IV insulin has a very short half-life, in order to prevent the recurrence of hyperglycemia and acidosis, it is important to overlap for 1–2 h the subcutaneous and IV insulin. If the patient has a history of type 1 diabetes mellitus, patient’s routine therapy can be resumed.
as long as an inadequate home regimen was not the reason for the hyperglycemia crisis. In newly diagnosed patients, a multidose insulin regimen should be started at a dose of 0.5–0.8 U/kg/day, the higher end of this range reserved for patients who have substantial degrees of insulin resistance as reflected by the insulin infusion requirements, prior history, body weight, and other physical features, such as acanthosis nigricans. Typically, however, the recent insulin infusion rates are not helpful in determining subcutaneous insulin doses, since they may be rapidly fluctuating, and with the resolution of gluco-toxicity, insulin requirements can be quite valuable.

A variety of subcutaneous insulin regimens are available from relatively straightforward (twice per day pre-mixed insulins) to relatively complex (e.g., long acting insulin in the evening and rapid-acting insulin with meals, the so-called basal-bolus strategy). The latter is likely to result in the best glycemic control, although it requires more understanding and participation by the patient. The use of insulin sliding scale alone should be discouraged, even as a transition, as it cannot provide the necessary insulin requirement in patients recovering from hyperglycemic crisis. Fingerstick glucose measurements before each meal and at night should be done after discontinuing the IV insulin to correct for possible fluctuations in insulin needs while in the hospital.

**Complications**

Hypoglycemia and hypokalemia are the most common iatrogenic complications during treatment for DKA and HHS. These can be prevented by very close monitoring (every 2–4 h) of potassium level and appropriate supplementation, adjustment of insulin dose, and use of dextrose-containing IV fluids.

Hyperchloremic non-anion gap metabolic acidosis is commonly seen after the resolution of DKA. It is usually explained by the high dose of chloride administered in IV fluids. This acidosis is self-limited and has no adverse clinical effects. Patients usually require several days to recover as the kidneys readjust bicarbonate production and acid secretion. The persistently low bicarbonate level due to hyperchloremic metabolic acidosis can be distinguished from persistent DKA due to inadequate insulin treatment by following the anion gap.

Cerebral edema is an uncommon but very serious complication of DKA and HHS treatment, associated with high mortality. For unclear reason, it is seen more commonly in children with DKA. Symptoms of cerebral edema include headache, lethargy, popillary changes, seizures, bradycardia, and cardiac arrest. The underlying mechanisms are not completely understood. Rapid decline in plasma osmolality and brain ischemia have been proposed as contributing mechanisms. Prevention of cerebral edema may be achieved by avoiding overzealous hydration and by maintaining plasma glucose ~200 mg/dL in DKA until the anion gap is closed. Patients should be carefully monitored for changes in mental and neurologic status.
Manitol infusion and mechanical ventilation are suggested for treatment of cerebral edema [28].

Noncardiogenic pulmonary edema can develop in DKA patients from excessive fluid replacement, even in patients without renal or cardiac problems. Pulmonary rales and an increased alveolar-arterial gradient should prompt a decrease in IV fluid rate and initiation of continuous pulse oxymetry.

**Prevention**

Many cases of DKA and HHS can be prevented by better access to medical care, proper patient education, and effective communication with healthcare provider during an intercurrent illness. Patients and their families should receive education about managing sick days. The use of urine ketone testing or combined home glucose-ketone meters can allow early recognition of impending ketoacidosis and possibly prevent hospitalization for DKA.

One of the most common precipitating factors for hyperglycemic crisis is discontinuation of insulin for economic reasons. This suggests that the current mode of providing health care has significant limitations. Thus, resources need to be directed towards funding better access to medical care and educational programs tailored to individual needs.

**References**

Endocrine Emergencies
Recognition and Treatment
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2014, X, 287 p. 50 illus., 25 illus. in color., Hardcover
A product of Humana Press