CHAPTER 163  ■  DISORDERED GLUCOSE METABOLISM

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PEARLS

■ Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic syndrome (HHS) result from dysregulation of normal glucose homeostasis caused by one of many precipitating conditions in patients with diabetes mellitus.
■ DKA (minimal intrinsic insulin secretion) is associated with hyperglycemia and ketone body formation, whereas HHS (intact intrinsic insulin secretion) is associated with hyperglycemia without ketone body formation.
■ Both DKA and HHS may present with various and vague complaints and progress to severe shock with cardiovascular collapse, severe metabolic acidosis, and death.
■ The treatment of DKA and HHS involves intravascular fluid resuscitation and insulin replacement with additional electrolyte supplementation.
■ Patients, during treatment of DKA and HHS, should be closely monitored for evidence of hypoglycemia, hyperglycemia, electrolyte disturbances, worsening lactic acidosis, intravascular volume overload, cerebral edema, acute respiratory distress syndrome (ARDS), severe coagulopathy, rhabdomyolysis, and thromboembolism.
■ Recent evidence has suggested that intensified glycemic control of intensive care unit (ICU) patients by using intravenous insulin infusions results in improved outcomes, including decreased mortality rate. While these observations led to dramatic changes in the management of diabetic patients in the ICU, the optimal range of glycemic control for patients with out systemic disorders of glucose metabolism and the clinical implication of the increased risk of iatrogenic hypoglycemia are currently under investigation.

Disordered glucose metabolism is a significant medical problem in patients in the outpatient, emergency room, ward, and intensive care settings. Diabetes mellitus (DM), the most important group of medical conditions resulting from disordered glucose metabolism, results in significant short-term and chronic morbidity, and is increasing in prevalence around the globe. In the United States alone, nearly 6% of the population (18.2 million people) is estimated to have this disease (1). Additionally, a significant number of these patients may not be diagnosed, which can further negatively impact their health. Despite increasing public awareness over the last few years, the prevalence of diabetes continues to increase (2).

Due to a combination of the sheer volume of patients with DM and the associated chronic health conditions, the disease is important for physicians, nurses, health care administrators, insurers, and public health advocates. More than 3.8 million hospitalizations per year are associated with diabetes, which is an increase of more than 70% over the last 20 years (3). Of note, the average length of stay is 6.5 days for these hospitalizations (3). Undeniably, these facts alone place an enormous economic and workforce burden on the entire health care system.

In addition to the many associated chronic health conditions developed by patients with DM, there are several acute and life-threatening conditions that also develop in these patients. Hyperglycemic emergencies, such as DKA and HHS, are important causes of morbidity and mortality in patients with DM who are admitted to the intensive care unit. Additionally, new research indicates that the prevention of hyperglycemia—with or without the diagnosis of diabetes—may be a key component of appropriate intensive care support of patients with numerous medical and surgical conditions.

DIABETIC KETOACIDOSIS

Since the discovery of insulin by Frederick Banting in 1921, outcomes for patients with diabetic ketoacidosis have steadily improved. Nevertheless, DKA remains a serious and potentially fatal complication of DM. Overall mortality from DKA is less than 5%; however, mortality increases substantially with extremes of age, the presence of coma, or the development of hypotension (4).

Hospital and ICU admissions for DKA and related conditions are increasing, and cause a significant burden on current health care delivery systems (5). With an annual incidence of 4.6 to 8 episodes per 1,000 patients with diabetes, DKA is the initial presentation of DM in up to 30% of patients overall, with approximately 40% of children and 17% of adults presenting in DKA without prior diagnosis of DM (4,5). While most patients presenting with DKA have type 1 DM, those with type 2 DM can also develop DKA during times of significant physiologic stress.

Pathophysiology

DKA results from a serious dysregulation of normal glucose homeostasis, leading to hyperglycemia and ketone body formation. Excess glucose and ketones launch a host of subsequent systemic sequelae. A deficiency, either relative or absolute, in insulin production, combined with an excess production of certain insulin counterregulatory hormones—glucagon, catecholamines, cortisol, and growth hormone, is responsible for these changes in serum glucose control. Most patients with type 1 DM who develop DKA have an absolute or
near-absolute insulin deficiency, whereas most patients with type 2 DM have either normal or elevated insulin levels (6,7). Because of the aberrant hormonal milieu, protein, lipid, and carbohydrate metabolism are all disrupted, and culminate in the production of proinflammatory cytokines, such as interleukin-6, interleukin-1β, interleukin-8, and tumor necrosis factor-α; free fatty acids; and plasminogen activator inhibitor-1, resulting in significant morbidity and mortality (8).

Normal glucose metabolism is typically tightly regulated to maintain a serum glucose concentration between 70 and 115 mg/dL (about 3.9–6.4 mmol/L) by carefully balancing glucose production in the liver and glucose utilization in peripheral tissues (9). Insulin, a 51-amino-acid peptide, is mainly responsible for this tight glucose control by stimulating hepatic glucose uptake and storage (glucose synthesis), and suppressing hepatic glucose production and glycogenolysis. Insulin also affects peripheral muscle tissue by promoting peripheral glucose uptake, promoting glycogen synthesis, and inhibiting peripheral glycogenolysis.

In DKA, either relative or absolute insulin deficiency combined with increased counterregulatory hormones (CRHs) promotes metabolic pathways opposite to insulin in both hepatic and peripheral tissues (10–13). These changes are typically the result of a precipitating event in patients with severely unbalanced DM (Table 163.1). Infection accounts for 30% to 50% of precipitating causes of DKA, with urinary tract and pulmonary infections making up the vast majority (14). Myocardial infarction, cerebrovascular accident, pulmonary embolism, pancreatitis, trauma, alcohol abuse, and drugs that affect carbohydrate metabolism can also precipitate DKA (15).

The end result of these changes is a substantial increase in serum glucose—through increased hepatic glucose production, glycogenolysis, and lipolysis—with inappropriately decreased peripheral insulin uptake (Fig. 163.1). DKA is also associated with ketosis, an additional product of worsening glucose homeostatic decompensation, which occurs as a result of increased lipolysis from increased action of hormone-sensitive lipase, an enzyme that causes increased triglyceride breakdown and free fatty acid release into the systemic circulation. Hormone-sensitive lipase is highly up-regulated during periods of insulin deficiency and elevations in CRH. Hepatic oxidation of free fatty acids induced by hormone-sensitive lipase produces ketone bodies, mainly β-hydroxybutyrate (β-OHB) and acetoacetate, strong acids that present a large hydrogen ion load to the body. The normal buffering systems are rapidly overwhelmed by the ongoing hydrogen ion load, and an anion gap acidosis develops.

Hyperglycemia and ketonemia produce a hypertonic intravascular environment, resulting in an intracellular water shift into the intravascular and interstitial compartments. The ensuing cellular dehydration is accompanied by electrolyte shifts as well. When the renal glucose reabsorption rate is exceeded, an osmotic diuresis of water and electrolytes occurs. Sodium, potassium, magnesium, calcium, chloride, and phosphate are all lost during this osmotic diuresis. Commonly, water and electrolyte deficits are compounded by poor oral intake and protracted vomiting. The effects of hypovolemia are responsible for the clinical picture as the depletion of the intravascular environment, resulting in an intracellular water shift and cellular dehydration.

Laboratory analysis is usually confirmatory of DKA in these patients (Table 163.2). A complete blood count, blood

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**TABLE 163.1**

**PRECIPITATING FACTORS IN DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC SYNDROME**

<table>
<thead>
<tr>
<th>INFECTION</th>
<th>Urinary tract infection</th>
<th>Pneumonia</th>
<th>Dental infection</th>
<th>Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>COEXISTING CONDITIONS</td>
<td>Acute myocardial infarction</td>
<td>Cerebrovascular accident</td>
<td>Pulmonary embolism</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>Renal failure/dialysis</td>
<td>Severe thermal injury</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td>Cushing syndrome</td>
<td>Cerebral vascular accident</td>
<td>Urinary tract infection</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td></td>
<td>Mesenteric thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MEDICATIONS**

- Calcium-channel blockers
- β-Blockers
- Chlorpromazine
- Cimetidine
- Diazoxide
- Diuretics
- Ethacrynic acid
- Phenytion
- Steroids

**SUBSTANCE ABUSE**

- Alcohol
- Cocaine

**UNDIAGNOSED DIABETES MELLITUS**

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**Presentation and Diagnosis**

The presentation and diagnosis of DKA is typically straightforward and relies on a thorough patient history, focused physical examination, and appropriate laboratory analysis. Patients typically report a history of poor glucose control and symptoms associated with hyperglycemia, such as polyuria, polydipsia, weight loss, and lethargy that may progress over the course of days to weeks. Nausea, vomiting, and abdominal pain are also common presenting complaints and frequently signify the progression from symptomatic hyperglycemia to overt DKA. Physical examination may reveal evidence of dehydration—for example, tachycardia, hypotension, prolonged capillary refill time, poor skin turgor, dry mucous membranes, and weight loss. Additionally, Kussmaul respirations (very deep, gasping breaths taken in response to severe metabolic acidosis), an acetone or fruity breath odor, depressed mental status, and even focal neurologic deficits or coma may also be seen.

Laboratory analysis is usually confirmatory of DKA in these patients (Table 163.2). A complete blood count, blood
Chapter 163: Disordered Glucose Metabolism

2431

Pathogenesis of DKA and HHS

Stress, Infection, and/or Insufficient Insulin Intake

Absolute insulin deficiency

- Lipolysis
- Triacylglycerol
- Hyperlipidemia

Relative insulin deficiency

- Glucagon
- Catecholamines
- Cortisol
- Growth hormone

Glucose utilization

- Gluconeogenic substrates

Proteolysis

- Protein synthesis

Gluconeogenesis

- Glucose utilization

- Glucose utilization

Hyperglycemia

- Glucosuria (osmotic diuresis)
- Ketoacidosis
- Hyperglycemia
- Hyperosmolarity

Hyperosmolarity

- Decreased fluid intake
- Impaired renal function

HHS

DKA

FIGURE 163.1. Pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic syndrome (HHS). FFA, free fatty acid. (Copyright © 2001, American Diabetes Association, from Diabetes Care 2001;24:131–153. Reprinted with permission from the American Diabetes Association.)

TABLE 163.2
DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS (DKA) AND HYPEROSMOLAR HYPERGLYCEMIC NONKETOATIC SYNDROME (HHS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>&lt;6.7</td>
<td>&gt;13.9</td>
<td>&gt;13</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.35–7.45</td>
<td>&lt;7.30</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
<td>22–28</td>
<td>&lt;15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Anion gap</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
</tbody>
</table>

nongap hyperchloremic metabolic acidosis may occur instead (17). Typically, the normal anion gap is between 7 and 9 mEq/L and reflects unmeasured ions in the serum. In patients with DKA, an elevated anion gap occurs because of the high ketone concentration. Other causes of anion gap–associated metabolic acidosis, which must be excluded during DKA evaluation, include alcoho1 ketosis, starvation ketosis, and lactic acidosis, as well as methanol, ethylene glycol, paraldehyde, and salicylate ingestion.

In patients with possible DKA, these other causes of anion gap–associated metabolic acidosis should be excluded through further history and laboratory analysis. For example, alcoho1 ketosis may present with profound metabolic acidosis, but typically has a characteristic history, an elevated blood alcohol content, and only mildly elevated serum glucose concentrations. Likewise, starvation ketosis is accompanied by a significant history and only mild acidosis. Ketonemia and ketonuria can both be assessed semiquanti-tatively with the nitroprusside reaction test. This test estimates the relative levels of acetoacetate and acetone in the blood, but does not detect the presence of β-OHB, potentially under-estimating the degree of ketosis. Because the ratio of β-OHB to acetoacetate may increase from 1:1 to as much as 5:1 dur-ing the development of DKA, β-OHB may represent the pre-

dominant ketone during illness (18). Of note, β-OHB moni-toring may significantly improve the diagnostic specificity in DKA patients with euglycemia or only mild hyperglycemia—as with prolonged vomiting, starvation, pregnancy, hepatic insufficiency, or following insulin administration—where blood glucose levels can be misleading (19).

**Management**

Management of DKA includes the phases of initial resuscitation, correction of hyperglycemia and resolution of ketosis, and treatment of any precipitating causes (Figs. 163.2 and 163.3). Following these phases, it is essential to also provide chronic therapy to prevent repeated episodes and secondary sequelae of diabetes mellitus.

As with all resuscitations, evaluation and treatment of air-way and breathing dysfunction should be done first. DKA can cause loss of protective airway reflexes, hypoxia, and hyper-ventilation. In patients with a severely depressed mental status, appropriate care should be taken to protect the airway so that pulmonary aspiration of gastric contents does not occur. If the patient’s Glasgow coma scale is 8 or less, or in situa-tions that require sedation and transport away from the acute

Management of Pediatric Patients (<20 years) with DKA or HHS

Complete initial evaluation. Start IV fluids: 10–20 mL/kg, 0.9 NaCl in the initial hour.

**IV Fluids**
- **Determine initial hydration status**
- **Hypovolemic shock**
  - Administer 0.9% NaCl (20 mL/kg/h) and/or plasma expander until shock resolved
  - If hypotension
    - Administer regular insulin 0.1 U/kg/h IV over 1 h
    - Continuous until acidosis clears (pH ≥ 7.3)
- Replace fluid deficit evenly over 48 h
- When serum glucose reaches 200 mg/dL
  - Decrease to 0.05 U/h/kg insulin replacement initiated

**Insulin**
- **IV route**
  - M/F no IV access
- **Monitor**
  - Administer 0.1 U/kg/h IV bolus followed by 0.1 U/h/kg SC or IV

**Potassium**
- **IV route**
  - **K⁺ > 3.5 mEq/L**
    - Monitor K⁺ hourly until K⁺ < 3.5 mEq/L
  - **K⁺ 2.5–3.5 mEq/L**
    - Do not give KCl
  - **K⁺ < 2.5 mEq/L**
    - Administer KCl 30–40 mEq/L in IV solution to maintain serum K⁺ at 3.5–4 mEq/L

**Assess need for bicarbonate**
- **pH ≤ 7.0**
  - Repeat pH after initial hydration bolus
  - Administer NaHCO₃ 2 mEq/kg added to 0.45% NaCl over 1 h
- **No HCO₃ indicated**
  - Monitor pH every 2–4 h until stable
  -Look for precipitating causes
  - Adjustments are to decrease the infusion rate to 250 mL/hour or to 4 to 14 mL/kg/hour, depending on the patient's hydration status and goal replacement volume. Depending on the patient's corrected serum sodium, isotonic saline is continued or changed to hypotonic saline. If the patient's corrected serum sodium is low, 0.9% saline solution should be continued as the replacement fluid; however, if the patient's corrected serum sodium is normal or elevated, the fluid should be changed to 0.45% saline solution in order to continue free water deficit replacement. Additionally, once plasma glucose levels reach 250 mg/dL, either 5% or 10% dextrose solution should be added to the replacement fluids to maintain serum glucose levels between 150 and 200 mg/dL, allowing the insulin infusion to continue until ketosis is reversed, and prevent the too rapid correction of hyperglycemic hyperosmolar nonketotic syndrome (HHS). (Copyright © 2001, American Diabetes Association, from *Diabetes Care* 2001;24:131–133. Reprinted with permission from the American Diabetes Association.)
Complications
Common complications encountered during DKA treatment include hypoglycemia and hypokalemia, various electrolyte...
Hypoglycemia and hyperglycemia are common complications of DKA treatment. Because intensive intravenous insulin therapy intentionally decreases blood glucose levels, reverses ketone body formation, and improves insulin sensitivity, it also places the patient at significant risk for hypoglycemia and its associated serious complications, including significant cognitive dysfunction, coma, and death. The incidence of serious hypoglycemic episodes associated with DKA treatment can be substantially decreased with the institution of low-dose insulin protocols, the addition of dextrose-containing solutions to intravenous management when the blood glucose concentration is felt to be related to an overly rapid correction of the hyperosmolar state. For this reason, current recommendations are to avoid potentially fatal complication that may occur at any time during the process of DKA. The disorder may be linked to the underlying cause of DKA as a source of infection, or the treatment phase with associated fluid resuscitation, fluid shifts, and changing osmotic gradients. Pulmonary aspiration of gastric secretions may also be responsible for the respiratory involvement. Patients with hypoglycemia, widened alveolar-to-arterial oxygen gradients, or other pre-existing cardiorespiratory conditions warrant close monitoring and possibly more judicious fluid resuscitation (14,41).

**TABLE 163.3**

**COMPLICATIONS OF DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC SYNDROME TREATMENT**

- Hypoglycemia
- Hypervolemia
- Electrolyte disturbances (hypokalemia, hyperkalemia)
- Hyperchloremic metabolic acidosis
- Cerebral edema
- Intravascular volume overload
- Noncardiogenic pulmonary edema
- Acute respiratory distress syndrome
- Bilirubinomylsis
- Thrombocytopenia

Hypoglycemia and hyperglycemia are common complications of DKA treatment. Because intensive intravenous insulin therapy intentionally decreases blood glucose levels, reverses ketone body formation, and improves insulin sensitivity, it also places the patient at significant risk for hypoglycemia and its associated serious complications, including significant cognitive dysfunction, coma, and death. The incidence of serious hypoglycemic episodes associated with DKA treatment can be substantially decreased with the institution of low-dose insulin protocols, the addition of dextrose-containing solutions to intravenous management when the blood glucose concentration is felt to be related to an overly rapid correction of the hyperosmolar state. For this reason, current recommendations are to avoid potentially fatal complication that may occur at any time during the process of DKA. The disorder may be linked to the underlying cause of DKA as a source of infection, or the treatment phase with associated fluid resuscitation, fluid shifts, and changing osmotic gradients. Pulmonary aspiration of gastric secretions may also be responsible for the respiratory involvement. Patients with hypoglycemia, widened alveolar-to-arterial oxygen gradients, or other pre-existing cardiorespiratory conditions warrant close monitoring and possibly more judicious fluid resuscitation (14,41).

**HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC SYNDROME**

HHS is a medical emergency that develops in response to one of many precipitating conditions (Table 163.3) in patients with type 2 DM. Among adults in the United States, the incidence of HHS is approximately 17.5 cases per 100,000 persons per year, and results in significant morbidity and mortality (42). The mortality rate from HHS is related directly to patient age, considering that mortality is, for example, less than 10% in patients younger than 75 years of age compared to 35% in patients older than 84 years of age (43,44).

In approximately 20% of patients presenting with HHS, this diagnosis is their initial presentation with type 2 diabetes (42). Additionally, the diagnosis is usually made after significant delay, and is made more complex because HHS can coexist with DKA in approximately 30% of patients (44).

**Pathophysiology**

The basic pathophysiological abnormality in HHS is a relative insulin deficiency caused by both an increase in peripheral insulin resistance and an increase in blood levels of counterregulatory hormones (Fig. 163.1) (44–46). These hormones—glucagon, cortisol, and growth hormone—and various catecholamines increase hepatic and renal glucose production, and further worsen peripheral tissue glucose utilization (44,45). Together, these defects cause an insidious but dramatic rise in serum glucose concentration, typically over days to weeks (45).

With increasing serum glucose concentration, an osmotic gradient develops between the intravascular and extravascular compartment (47). Because water moves from the extravascular compartment down this osmotic gradient, both intracellular dehydration and a transiently increased intravascular volume with relative serum hyperosmolality can occur. As the serum glucose concentration continues to rise, osmotic diuresis causes profound decreases in intravascular volume, coupled with losses of vital electrolytes such as sodium, potassium,
phosphate, and magnesium (43). This large intravascular volume loss can result in life-threatening end-organ hypoperfusion and nonketotic metabolic acidosis. Compared to DKA, ketones are minimally produced in patients with HHS likely due to the ability of the pancreas to secrete insulin. The amount of insulin, while not sufficient to prevent hyperglycemia in these patients, does prevent fatty acid lipolysis and the formation of ketone bodies and development of ketosis.

Presentation and Diagnosis

Because patients with HHS typically fail to develop ketoacidosis, the time from onset to diagnosis and treatment can be significantly longer than in patients with DKA (45). The clinical diagnosis of these patients, therefore, requires a high clinical suspicion to promptly recognize the signs and symptoms of HHS and institute appropriate diagnostic and treatment modalities.

Patients with suspected HHS may initially exhibit nausea/vomiting, visual disturbances, muscle weakness, and leg cramps (48). Left untreated, these patients eventually develop confusion, lethargy, hemiparesis, seizures, and coma (49). Physical examination may reveal both signs of profound dehydration—such as decreased skin turgor and dry mucous membranes—as well as abdominal distension from gastroparesis (50).

Initial laboratory evaluation in patients with suspected HHS should include serum glucose, ketones, electrolytes, and creatinine concentration; serum measured and calculated osmolality; urinalysis; and appropriate empiric bacterial and fungal cultures (Table 163.2) (45). Because these patients can have significantly elevated serum glucose concentrations—as high as or higher than 1,000 mg/dL, the serum osmolality can be quite high and seems to correlate with neurologic symptoms (51).

Management

The treatment goals for HHS include aggressive intravascular fluid replacement, insulin administration to correct hyperglycemia, appropriate electrolyte replacement, and, if indicated, respiratory system support (Fig. 163.4). Ultimately, effective patient education and long-term patient support are also important.

HHS treatment is typically undertaken in two phases. The first is the acute—emergency—phase and consists of rapid restoration of circulatory volume and electrolyte deficits with

Management of Adult Patients with HHS

- Complete initial evaluation. Start IV fluids: 1.0 L of 0.9% NaCl per hour initially.
- IV Fluids: Determine hydration status
  - Hypovolemic shock
  - Administer 0.9% NaCl (1.5 L/h) and/or plasma expanders
  - Hemodynamic monitoring
  - Evaluate corrected serum Na+
    - Serum Na High
    - Serum Na Normal
    - Serum Na low
  - If serum Na < 135 mEq/L, give 5% dextrose with 0.45% NaCl and decrease insulin to 0.05–0.1 U/kg/h to maintain serum glucose between 250–300 mg/dL until plasma osmolality is ≥315 mOsm/kg and patient is mentally alert.
  - If serum Na ≥ 135 mEq/L, give 0.45% NaCl until serum Na ≥ 135 mEq/L.
  - If serum Na < 135 mEq/L, give 0.9% NaCl until serum Na ≥ 135 mEq/L.
- Insulin: Regular, 0.15 U/kg as IV bolus
  - Check serum glucose hourly; if serum glucose does not fall by at least 50 mg/dL in first hour, then double insulin dose hourly until glucose falls at a steady hourly rate of 50–70 mg/dL.
- Potassium: If serum K+ is < 3.3 mEq/L, hold insulin and give 40 mEq K+ (2/3 as KCl and 1/3 KPO4) until K+ ≥ 3.3 mEq/L.
  - If serum K+ ≥ 3.3 but < 5.5 mEq/L, give 20–30 mEq K+ in each liter of IV fluid (2/3 as KCl and 1/3 KPO4) to keep serum K+ at 4–5 mEq/L.
  - If serum K+ ≥ 5.0 mEq/L, do not give K+, but check potassium every 2 h.

Check Chem 7 every 2–4 h until stable. Look for precipitating causes.

In addition to the electrolyte abnormalities discussed above, hypokalemia and hypophosphatemia. Phosphate may be an ideal replacement infusion to correct both. If phosphate replacement is necessary, potassium absence of decreased cardiac or respiratory function and ane-

to show a definitive benefit to phosphate replacement in the

to 40 mEq/hour—may be necessary. Hypophosphatemia may

to 40 mEq/hour to reduce the risk of acute cerebral edema.

The cornerstone of therapy for HHS is intravenous insulin
given to restore normal peripheral glucose uptake, suppress
lipolysis, and decrease hepatic glucoseogenesis. Complications
of insulin therapy include hypoglycemia, hypokalemia (insulin
infusion should not begin with serum potassium less than
3.5 mEq/dL), and hypophosphatemia. Insulin should be ini-
tiated with 0.1 unit/kg body weight as an intravenous bolus of 0.15 unit/kg, followed by a continuous infusion of 0.1 unit/kg/hour with a goal glucose decrease of 50 to 75 mg/dL/hour. While the patient is receiving intravenous insulin, the glucose should be monitored every 1 to 2 hours via either capillary or serum samples. Once the serum glucose decreases to 250 mg/dL, dextrose should be added to the intravenous fluid administration, and the insulin infusion should be decreased to 0.05 to 0.1 unit/kg/hour.

Electrolyte replacement is also an important component to
the management of HHS. Hypokalemia can develop during HHS treatment because insulin administration causes an in-
tracellular shift of potassium ions from the extracellular com-
partment. Additionally, the ongoing osmotic diuresis can cause a dramatic depletion of total body potassium stores; this loss can exceed 400 mEq in severe HHS. For this reason, electro-
cardiographic monitoring should be utilized during this phase
of therapy, and aggressive potassium replacement—with up
to 40 mEq/hour—may be necessary. Hypophosphatemia may
do be secondary to the ongoing osmotic diuresis. Re-
placement of phosphate during HHS treatment seems prudent; however, several prospective randomized studies have failed to show a definitive benefit to phosphate replacement in the absence of decreased cardiac or respiratory function and ane-
mia (36,52). If phosphate replacement is necessary, potassium phosphate may be an ideal replacement infusion to correct both hypokalemia and hypophosphatemia.

Complications

In addition to the electrolyte abnormalities discussed above, complications from HHS include pancreatitis, rhabdomyol-
ys, thromboembolism, hyperchloremic metabolic acidosis, cerebral edema, acute gastric dilatation, and ARDS (Table

Chapter 163: Disordered Glucose Metabolism

Over the last decade, multiple published studies (Table 163.4) suggested that intensified glycemic control of ICU pa-
tients by using intravenous insulin infusion results in improved outcomes, including decreased mortality rate. While these ob-
terapy with intravenous insulin produced a

SUMMARY

Future directions in DKA and HHS therapy involve further refinements in protocols and therapies aimed to improve the hyperglycemia, acidosis, and electrolyte imbalances while mini-

GLYCEMIC CONTROL AND INSULIN THERAPY IN THE

INTENSIVE CARE UNIT

Over the last decade, multiple published studies (Table 163.4) suggested that intensified glycemic control of ICU pa-
tients by using intravenous insulin infusion results in improved outcomes, including decreased mortality rate. While these ob-
terapy with intravenous insulin produced a
populations. However, several important differences should be noted. In some cases, all the participants had diabetes, whereas in others, most participants were nondiabetic. In addition, there were remarkable differences in the range of blood glucose levels achieved. For instance, the glucose levels of the control group of the Leuven studies were similar to—and in some cases, lower than—the levels in the intensive treatment groups of the other studies. However, the differences in blood glucose levels between the control and intensive treatment groups were similar in all five studies. Furthermore, there was a comparable improvement in mortality rate in the critically ill patients who remained in intensive care for secondary to a defect in the adherence properties of polymorphonuclear leukocytes (63,64). An analysis of data from the 363 patients who remained in intensive care for >7 days in the Leuven I study revealed a strong relationship between serum triglyceride (TG) and ICU mortality rate by univariate analysis (an approximate 400% increase in mortality rate in patients with TAG >3.4 mmol/L compared with individuals with TAG <1.1 mmol/L). Accordingly, an alternative explanation for the benefits of insulin infusion is that they were not a direct consequence of lowering glucose, but rather due to effects of insulin on lipid control, especially in patients who received PN (65).

Another important observation is that the two studies that achieved by far the lowest glucose levels in the intensively treated patients were also the only two studies in which parenteral nutrition (PN) was often associated with hyperglycemia and hypertriglyceridemia (62). Furthermore, there is considerable evidence that PN can be responsible for other adverse outcomes in critically ill patients. In a meta-analysis of 27 studies comparing PN with enteral nutrition and involving >1,800 patients, Braunschweig et al. found a 50% higher incidence of infection in participants receiving PN, but no difference in mortality rate (62). The implications of these findings in interpreting the Leuven I study are obvious. Patients in the Leuven I study received PN, a treatment known to increase infection rates, and when glucose level was lowered with insulin infusion to an average of 5.7 mmol/L, an improvement in mortality rate, based mostly on a reduction in infection rate, was observed. Hence, the administration of intravenous insulin in this study merely reduced infectious complications to a level that would have been observed if PN had not been otherwise given.

Furthermore, one of the mechanisms that may explain an increased rate of infection in diabetic individuals and hospitalized patients with hyperglycemia is impaired immune function secondary to a defect in the adherence properties of polymorphonuclear leukocytes (63,64). A study from the 363 patients who remained in intensive care for >7 days in the Leuven I study revealed a strong relationship between serum triglyceride (TG) and ICU mortality rate by univariate analysis (an approximate 400% increase in mortality rate in patients

### Table 163.4

<table>
<thead>
<tr>
<th>Study</th>
<th>DRGAMI</th>
<th>Leuven I</th>
<th>Portland</th>
<th>Stanford</th>
<th>Leuven II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Acute MI (N = 620)</td>
<td>Surgical (N = 1,548)</td>
<td>CABG (N = 3,554)</td>
<td>Medical ICU (N = 1,600)</td>
<td>Medical ICU (N = 767)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>100%</td>
<td>13%</td>
<td>100%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Decrease in mortality rate</td>
<td>30%</td>
<td>34%</td>
<td>31%</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>Reason for reduced mortality rate</td>
<td>N/K</td>
<td>Sepsis</td>
<td>HF, VT, VF</td>
<td>N/K</td>
<td>Multiple</td>
</tr>
<tr>
<td>Mean glucose (mmol/L)</td>
<td>17 (&lt;3.0)</td>
<td>5.2 (&lt;2.2)</td>
<td>0.8 (&lt;3.3)</td>
<td>1.3 (&lt;3.3)</td>
<td>2.5 (&lt;2.2)</td>
</tr>
<tr>
<td>Intensive treatment</td>
<td>9.2</td>
<td>5.7</td>
<td>9.8</td>
<td>7.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Conventional treatment</td>
<td>12.0</td>
<td>8.5</td>
<td>11.8</td>
<td>8.4</td>
<td>8.6</td>
</tr>
</tbody>
</table>

**TABLE 163.5**

**THE SURVIVING SEPSIS CAMPAIGN 2008 CONSENSUS RECOMMENDATION ON GLUCOSE CONTROL DURING SEVERE SEPSIS**

1. Following initial stabilization, intensive care unit patients with severe sepsis and hyperglycemia to receive intravenous insulin therapy to reduce blood glucose levels (grade 1B).

2. Validated protocol to be used for insulin dose adjustments and targeting glucose levels to the <150 mg/dL range (grade 2C).

3. All patients receiving intravenous insulin to receive a glucose caloric source in addition to monitoring blood glucose values every 1–2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter (grade 1C).

4. Caution taken if using point-of-care testing for capillary blood glucose as it may overestimate arterial blood or plasma glucose values (grade 1B).

carry the risk of hypoglycemia, which is potentially more dif-
ficult to detect (59).

To address the above concerns, a large RCT in 20 ICUs in
Australia and New Zealand is currently under way to com-
pare target serum glucose levels of 4.5 to 6.0 mmol/L (80–110
mg/dL) versus 8 to 10 mmol/L (140–180 mg/dL). This trial will
provide information about the effect of normoglycemia in a
heterogenous group of critically ill patients. In addition, it
will recruit >6,000 patients and most likely will produce ≥500,000
glucose measurements that subsequently can be used to re-
solve some of the many unknown dimensions of glycemic control
and its consequences for ICU patients.

In the meantime, several recommendations for glycemic
control in the ICU have been suggested in the most current Sur-
viving Sepsis Campaign (Table 16.3.5) (69). These recommen-
dations are intended to provide some direction for the clinician
caring for ICU patients with severe sepsis while awaiting results
from the ongoing studies on potential differences in outcomes
with different glucose targets and various insulin protocols.

Until the full results of the ongoing studies become avail-
able, intensive insulin therapy to all ICU patients remains un-
supported, and should be viewed with a healthy degree of sci-
entific skepticism.

**SUMMARY**

The weight of available data indicates that intensified insulin
treatment of the critically ill is associated with impressive re-
ductions in mortality rate. Therefore, the value of intensive
insulin treatment should not be in doubt. However, the ques-
tion remains if the available data justify a glycemic target of
6.1 mmol/L. As pointed out above, the reduction in mortal-
ity reported in Leuven can be secondary to lipid, rather than
glucose, control. Since these are mere associations, additional
research will be required in which lipid levels are maneuvered
more directly in order to assess whether nonglucose effects of
insulin are, in fact, responsible for the apparent benefits of in-
sulin. In addition, since the use of PN in the Leuven I study
may impose additional constraints on its subjects, intensive insulin
treatment in this study may merely have counteracted the ad-
verse effects of PN. Finally, considering that the Leuven I study
was not designed to compare different glycemic targets with
intensive insulin treatment, judgments concerning whether a
goal of 6.1 mmol/L will produce better outcomes than a higher
goal must await the results of ongoing studies.

Furthermore, since hypoglycemia is likely to be more fre-
quent and more severe with lower glucose targets, it seems
prudent to adjust the dose of intravenous insulin to target glu-
cose levels ≥5.0 and ≤8.3 mmol/L.

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Section XVII: Endocrine Disease and Dysfunction