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Management of Hyperglycemic Crises: Diabetic ketoacidosis and hyperglycemic hyperosmolar state

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Introduction

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the most serious and life-threatening hyperglycemic emergencies in patients with diabetes. Although DKA and HHS are often discussed as separate entities, they represent points along a spectrum of hyperglycemic emergencies due to poorly controlled diabetes. Both DKA and HHS can occur in patients with type 1 and type 2 diabetes; however, DKA is more common in young people with type 1 diabetes (T1D) and HHS is more frequently reported in adult and elderly patients with type 2 diabetes (T2D). In many patients, features of the two disorders with ketoacidosis and hyperosmolality may also co-exist. The frequency of DKA has increased by 30% during the past decade, with more than 140,000 hospital admissions per year in the United States [1,2]. The rate of hospital admissions for HHS is lower than for DKA, accounting for less than 1% of all diabetes-related admissions [3,4]. Both disorders are characterized by insulinopenia and severe hyperglycemia. Early diagnosis and management is paramount to improve patient outcomes. The mainstays of treatment in both DKA and HHS are aggressive rehydration, insulin therapy, electrolyte replacement, and discovery and treatment of underlying precipitating events. Herein we review the epidemiology, pathogenesis, diagnosis, and provide practical recommendations for the management of patients with hyperglycemic emergencies.

Historical Review of Diabetic Comas

The first detailed clinical description of diabetic coma in an adult patient with severe polydipsia, polyuria, and a large amount of glucose in the urine followed by progressive decline in mental status and death was reported by August W. von Stosch in 1828 [5]. This publication was followed by several case reports describing young and adult patients, with newly diagnosed or with established diabetes, who presented with abrupt clinical course of excessive polyuria, glycosuria, coma and death [6–8]. In 1874, The German physician Adolf Kussmaul reported that many cases of diabetic coma were preceded by deep and frequent respiration and severe dyspnea [9,10]. Kussmaul breathing rapidly became one of the hallmarks of diabetic coma. Shortly after that, it was reported that in many of these patients, the urine contained large amounts of acetoacetic acid and β-hydroxybutyric acid [11,12]. Dr.

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Julius Dreshfeld in 1886, was first to provide a comprehensive description of the two different categories of diabetic coma [13], one with Kussmaul breathing and positive ketones and the other, an unusual type of diabetic coma in older, well-nourished individuals, characterized by severe hyperglycemia and glycosuria but without Kussmaul breathing, fruity breath odor, or a positive urine acetone test.

Prior to the discovery of insulin in 1921, the mortality rate of patients with diabetic ketoacidosis was over 90%. The first successful case of DKA treated with insulin was reported by Banting and Best in a 14 year old boy who presented with a blood glucose of 580 mg/dL and strongly positive urinary ketones at the Toronto General Hospital in 1923 [14]. They reported a dramatic improvement in glycosuria along with disappearance of acetone bodies in the urine after a few doses of pancreatic extract injections[14]. Following the discovery of insulin, mortality rate associated with diabetic comas fell dramatically to 60% in 1923 and 25% by 1930's [15], 7–10% in the 1970s [16,17] and is currently less than 2% in patients for DKA [1,18,19] and between 5–16% in patients with HHS [20,21].

Epidemiology

Even though DKA occurs more commonly in patients with autoimmune T1D, the cumulative number of cases of DKA reported in patients with T2D represents at least a third of all cases [22]. Global epidemiological studies have reported on the incidence of DKA among patients with T1D. An analysis from the Prospective Diabetes Registry in Germany including 31,330 patients reported a DKA admission rate of 4.81/100 patient-years (95% CI, 4.51–5.14) [23]. Individuals with the highest risk included those with high HbA1c, longer diabetes duration, adolescents, and girls [23]. Multinational data from 49,859 children (<18 years) with T1D across three registries and five nations similarly found higher odds of DKA among females (odds ratio [OR] 1.23, 99% CI 1.10–1.37), ethnic minorities (OR 1.27, 99% CI, 1.11–1.44), and among those with HbA1c ≥7.5% (OR 2.54, 99% CI, 2.09–3.09 for HbA1c from 7.5 to <9% and OR 8.74, 99% CI, 7.18–10.63 for HbA1c ≥9.0%) [24]. Data from the T1D Exchange Clinic Network including 2,561, shows that young adults (18–25 years) have the highest occurrence of DKA (~5%) defined as ≥1 event in prior 3 months [25]. HHS typically occurs in older patients with type 2 diabetes [20]; however, it is being recognized as an emerging problem in children and young adults [26].

Similar mortality rates have been reported in European countries, but the reported mortality continues to be higher than 10% in Indonesia and sub-Saharan African countries [27,28]. HHS occurs most commonly in older patients with T2D with an intercurrent illness such as infection, surgery or ischemic events, and is associated with higher mortality rate than DKA. Mortality in patients with HHS is reported between 5 and 16%, which is about 10 times higher than the mortality in patients with DKA [20,21,29]. The cause of death in patients with DKA and HHS rarely results from the metabolic complications of hyperglycemia or metabolic acidosis but relates to the underlying precipitating cause, severity of dehydration, and advanced age [1,4,30].

Treatment of patients with DKA and HHS is associated with substantial mortality and healthcare costs. DKA is the leading cause of mortality among children and young adults

with T1D, accounting for ~50% of all deaths in diabetic patients younger than 24 years of age [1]. In the United States, the overall inpatient DKA mortality is <1% [1,2] but a higher rate is reported among elderly patients with life-threatening illnesses [1,2,31,32]. Similar mortality rates have been reported in European countries, but the reported mortality continues to be higher than 10% in countries with limited acute care resources [28]. A history of recurrent DKA episodes increases substantially the long-term mortality after discharge, particularly among young, socially disadvantaged adults with very high HbA1c [33]. In a retrospective review from the United Kingdom, the long-term mortality following a single episode of DKA was 5.2% (4.1 [2.8–6.0] years of follow-up) compared with 23.4% in those with recurrent DKA admissions (2.4 [2.0–3.8] years of follow-up) (HR 6.18) [33]. Inpatient mortality has been reported in 5–16% of patients with HHS, a rate that is ~10-fold higher than that reported for DKA [20,21,29]. The prognosis and outcome of patients with HHS is determined by the severity of dehydration, presence of co-morbidities and advanced age. In addition, patients with history of HHS are at significant risk of mortality after hospitalization, in particular those with multiple episodes. Compared to patients with diabetes without HHS, a recent study reported that after adjustment for age, sex, selected comorbidities, and monthly income, the mortality hazard ratio was 2.8 and 4.5 times higher in subjects with one episode and two or more episodes of hyperglycemic crisis, respectively [34]. National data shows a decline in death related to both hyperglycemic crises with and absolute decline of 529 deaths in the period of 1990 to 2010 (2.7 fewer cases per 10,000; 95% CI, 2.4 to 3.0) [35].

Treatment of hyperglycemic crises represents a substantial economic burden, with an estimated total annual hospital cost of $2.4 billion[1]. In the US, it is estimated that DKA episodes represent more than $1 of every $4 spent on direct medical care for adult patients with T1D and $1 of every $2 in those patients with multiple DKA episodes [36].

Precipitating Cause

The most common precipitating causes of DKA reported in different epidemiological studies worldwide are shown in Table 1. DKA is the initial presentation of diabetes in ~15% to 20% of adults and in ~30 to 40% of children with T1D [4,37,38]. Infection is the most common cause of DKA around the world; however, poor adherence to insulin treatment is the most common precipitating cause of DKA in young patients with T1D and in inner city populations in the U.S. [39–41]. According to a recent report from a safety net hospital in Atlanta, insulin discontinuation accounted for 56% of patients with their first and 78% of patients with multiple DKA episodes [39]. Other potential precipitants of DKA included infections (14%) and non-infectious illness (4%) [39] such as acute myocardial infarction, neurovascular accidents, alcohol use, and pancreatitis [42]. Psychological risk factors including depression and eating disorders have been reported in up to 20% of recurrent episodes of ketoacidosis in young patients [39,43,44]. Insulin pump malfunction has long been recognized as a cause of DKA [45,46] due to the short acting insulin formulation used in pumps; however, this is not a common event with newer improved pump technology [47,48].

Urinary tract infection and pneumonia are common precipitating causes of HHS [46,49], as well as acute cardiovascular events and other concomitant medical illnesses [20,50]. Poor

adherence to medical therapy and new diabetes onset are less common precipitating cause of HHS than in DKA[49].

Several medications that altered carbohydrate metabolism may precipitate the development of DKA and HHS including glucocorticoids, beta-blockers, thiazide diuretics, certain chemotherapeutic agents [50,51], and atypical antipsychotics [52–55]. One large retrospective review from the UK reported that hyperglycemic emergencies occurred at a rate of 1–2 per 1,000 person-years following initiation of antipsychotics [56]. Of the antipsychotics, olanzapine and resperidone where associated with the highest risk [56].

Recently, the sodium glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral antidiabetic agents that lower plasma glucose by inhibiting proximal tubular reabsorption of glucose in the kidney have been associated with DKA in patients with T1D and T2D [57,58]. An atypical presentation of DKA, which can lead to delayed recognition and treatment, has been referred to as “euglycemic DKA” due to only mild to moderate elevations in blood glucose reported in many cases [59]. Compiled data from randomized studies with the use of SGLT2-inhibitors reported a very low incidence of DKA in patients with T2D ~0.07% [60,61]; however, the risk of ketosis and DKA is higher in patients with T1D. About 10% of patients with T1D treated with SGLT2-inhibitors develop ketosis and 5% require hospital admission for DKA [59]. Potential mechanisms have been proposed, including higher glucagon levels, reduction of daily insulin requirement leading to a decrease in the suppression of lipolysis and ketogenesis, and decreased urinary excretion of ketones [62,63].

Pathophysiology

The two most important pathophysiologic mechanisms for DKA and HHS are significant insulin deficiency and increased concentration of counter-regulatory hormones such as glucagon, catecholamines, cortisol, and growth hormone, Figure 1 [6465,66]. The insulin deficiency of DKA can be absolute in patients with T1D or relative as observed in patients with T2D in the presence of stress or intercurrent illness [67]. Insulin deficiency coupled with increased counterregulatory hormones lead to increased hepatic glucose production due to increased hepatic gluconeogenesis and glycogenolysis [68], as well as reduced glucose utilization in peripheral tissues, in particular muscle [69]. Insulinopenia also leads to activation of hormone-sensitive lipase and accelerated breakdown of triglycerides to free fatty acids (FFA)[70]. In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon [71,72] and increased glucagon/insulin ratio [73]. The increased glucagon/insulin ratio lowers the activity of malonyl coenzyme A (CoA), the enzyme that modulates movement of FFA into the hepatic mitochondria where fatty acid oxidation takes place. The increased production of ketone bodies (acetoacetate and β-hydroxybutyrate), two strong acids, leads to reduction of bicarbonate and metabolic acidosis.

Several mechanisms have been proposed to explain the absence or minimal presence of ketone bodies in patients with HHS including higher levels of circulating insulin, lower levels of counter-regulatory hormones and FFAs, and inhibition of lipolysis by the hyperosmolar state (Figure 1). Of them, higher insulin secretion appears to be the most important mechanism to prevent ketosis in HHS compared to patients with DKA [66]. This is

due to the fact that the antilipolytic effect of insulin is about one tenth that of glucose utilization.

Oxidative stress/Inflammation.

Several experimental and clinical studies have shown that development of hyperglycemia and ketoacidosis result in an inflammatory state characterized by an elevation of pro-inflammatory cytokines and increased oxidative stress markers [74,75]. Severe hyperglycemia-induced macrophage production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF α), interleukin (IL)-6 and IL-1β, and C-reactive protein, which inturn lead to impaired insulin secretion as well as reduced insulin sensitivity [75–77]. Elevation in FFAs also increases insulin resistance as well as impaired nitric oxide production in endothelial cells and endothelial dysfunction [78]. The increased inflammatory response, oxidative stress and generation of reactive oxygen species (ROS) can lead to capillary perturbation and cellular damage of lipids, membranes, proteins, and DNA[75,79].

Diagnosis of DKA

Signs and Symptoms.

Patients with DKA often present with a short clinical course characterized by fatigue and classic symptoms of hyperglycemia: polyuria, polydipsia, and weight loss. Gastrointestinal complaints are common with diffuse abdominal pain reported in 46% of patients and nausea and vomiting in up to two-third of patients [42]. About half of the patients present with lethargy and stupor, but less than 25% present with loss of consciousness [1]. On physical examination, patients often present with signs of dehydration with dry mucous membranes and poor skin turgor, tachycardia or hypotension. Patients in DKA may exhibit Kussmaul respirations and a classic fruity (acetone) breath odor (Table 2).

Laboratory Findings.

The syndrome of DKA consists of the triad of hyperglycemia, ketonemia and metabolic acidosis (Table 3). The American Diabetes Association classifies DKA by severity as mild, moderate, or severe depending on the degree of acidosis (along with decrease in bicarbonate) and altered sensorium [1]. Most patients with DKA present with mild to moderate DKA with blood glucose > 250 mg/dL, bicarbonate between 10 and <18 mEq/L, arterial pH < 7.3, high ketones in urine or blood, and increased anion gap metabolic acidosis > 12.

Anion gap is calculated with the formula = sodium [Na^+] – (chloride [Cl-] + [HCO_3^-]. Although the majority of patients present with plasma glucose levels > 250 mg/dL, some patients exhibit only mild elevations in plasma glucose levels (termed ‘euglycemic DKA’) [80]. This phenomenon has been reported during pregnancy, in patients with prolonged starvation, alcohol intake, pregnancy, partially treated patients receiving insulin, and more recently in the setting of SGLT-2 inhibitor use [59,81,82].

The key diagnostic criterion is an elevation in circulating total blood ketone and high anion gap metabolic acidosis >12. Assessment of ketonemia can be performed by the nitroprusside

reaction in urine or serum, which provides a semi-quantitative estimation of acetoacetate and acetone levels. The nitroprusside test is highly sensitive, but it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of β-hydroxybutyrate, the main metabolic product in ketoacidosis [69,83]. Therefore, direct measurement of serum β-hydroxybutyrate is preferred for diagnosis [84].

Diagnosis of HHS

Symptoms and Signs.

The majority of patients with HHS present with a history of polyuria, polydipsia, weakness, blurred vision, and progressive decline in mental status [50,85]. The typical patient with HHS is older than 60 years of age with an infection or acute illness who has delayed seeking medical attention. On physical examination, similar to DKA, patients with HHS frequently have clear signs of dehydration, dry mucous membranes and poor skin turgor, or hypotension [50].

Laboratory Findings.

The diagnostic criteria for HHS includes a plasma glucose of over 600 mg/dl, and effective osmolality >320 mOsm/kg, and the absence of ketoacidosis [1]. Effective osmolality is calculated with the formula = sodium ion (mEq/L) x 2 + glucose (mg/dL)/18. Although by definition, HHS is characterized by a pH > 7.3, bicarbonate > 18 mEq/L, and negative ketone bodies, mild to moderate ketonemia may be present. Patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or to an increase in serum lactate levels or renal failure [21]

Common Laboratory Pitfalls.—Patients with DKA frequently present with significant leukocytosis with white cell counts in the 10,000–15,000 mm^3 range. A leukocyte count greater than 25,000 mm^3 or the presence of greater than 10% neutrophil bands is seldom seen in the absence of bacterial infection [66,86]. In ketoacidosis, leukocytosis is attributed to stress, dehydration, and demargination of leukocytes.

The admission serum sodium may be low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose above 100 mg/dL [1]. An increase in serum sodium concentration in the presence of severe hyperglycemia indicates a profound degree of dehydration and water loss.

The admission serum potassium concentration is usually elevated in patients with DKA and HHS66. In a several studies [1,39,87], the mean serum potassium in patients with DKA and HHS was 5.6 mEq/l and 5.7 mEq/L, respectively. These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to insulin deficiency and hypertonicity as well as academia in DKA [88]. It is important to keep in mind that during insulin treatment and fluid administration, potassium levels decrease due to a shift back to the intracellular space, which may result in hypokalemia.

Similarly, serum phosphate levels in patients with DKA do not reflect the actual body deficit that uniformly exists, as phosphate shifts from the intracellular to the extracellular space due to insulin deficiency, hypertonicity, and catabolic state. Dehydration also can lead to increases in total serum protein, albumin, amylase, and creatinine phosphokinase concentration in patients with hyperglycemic crises.

Not all patients who present with ketoacidosis have DKA. Patients with chronic ethanol abuse with a recent binge culminating in nausea, vomiting and acute starvation may present with alcoholic ketoacidosis. The key diagnostic feature that differentiates diabetic and alcohol-induced ketoacidosis is the concentration of blood glucose [89]. The presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of alcoholic ketoacidosis. In addition, some patients with decreased food intake and caloric intake lower than 500 calories/day for several days may present with starvation ketosis. Patients with starvation ketosis rarely present with a serum bicarbonate concentration less than 18 mEq/L because of the slow onset of ketosis that allows increased ketone clearance by peripheral tissue (brain and muscle) and enhancement of the kidney's ability to excrete ammonia to compensate for the increased acid production [90].

Management of hyperglycemic crises

The American Diabetes Association algorithm for the management of hyperglycemic emergencies is shown in Figure 2 [1]. Similar therapeutic measures are recommended for the treatment of DKA and HHS. In general, treatment goals include correction of dehydration, hyperglycemia and hyperosmolality, electrolyte imbalance, increased ketonemia, and identification and treatment of precipitating event(s). The average time to resolution between 10–18 hours for DKA [91,92] and ~9–11 hours for HHS [4]. During treatment, frequent monitoring of vital signs, volume and rate of fluid administration, insulin dosage, and urine output are needed to assess response to medical treatment. In addition, laboratory measurements of glucose and electrolytes, venous pH, bicarbonate, and anion gap should be repeated every 2–4 hours [93].

Most patients with uncomplicated DKA can be treated in the emergency department or in step-down units, if close nursing supervision and monitoring is available. Several studies have failed to demonstrate clear benefits in treating DKA patients in the ICU compared to step-down units [94–96]. The mortality rate, length of hospital stay, or time to resolve ketoacidosis are similar between patients treated in ICU and non-ICU settings. In addition, ICU admission has been associated with more laboratory testing and higher hospitalization cost in patients with DKA [36,94]. Patients with mild to moderate DKA can be safely managed in the emergency department or in step-down units, and only patients with severe DKA or those with a critical illness as precipitating cause (i.e., myocardial infarction, gastrointestinal bleeding, sepsis) [1,97] should be treated in the ICU. Because patients with HHS frequently present with altered mental status and have significantly higher mortality than patients with DKA, we recommend that patients with HHS should be managed in the ICU.

Fluid Therapy

Intravenous (IV) fluids are a critical aspect of treatment of hyperglycemic emergencies. Treatment with IV fluids alone expands intravascular volume, restores renal perfusion and reduces insulin resistance by decreasing circulating counter-regulatory hormone levels [64]. Isotonic saline (0.9% NaCl) is the preferred solution and is given at an initial rate of 500–1000 mL/hour during the first 2–4 hours. A study comparing two IV fluid regimens with sodium chloride and lactate ringers found no significant difference in time to resolution of DKA, but the time to correct hyperglycemia was significantly longer in the lactate ringers group [98]. After intravascular volume depletion has been corrected, the rate of normal saline infusion should be reduced to 250 mL/h or changed to 0.45% saline (250–500 mL/h) depending upon the serum sodium concentration and state of hydration [1]. Once the plasma glucose level reaches ~200 mg/dL (11.1 mosm/L), replacement fluids should contain 5–10% of dextrose to allow continued insulin administration until ketonemia is corrected, while avoiding hypoglycemia [99]. Adequate fluid resuscitation is of particular importance in management of HHS, as many of them, may see improvement in or resolution of mental status changes with correction of fluid deficits [85].

Potassium

Metabolic acidosis and insulin deficiency both lead to extracellular movement of potassium. Thus, although serum potassium levels may be normal or elevated in DKA, patients are actually total body depleted. Similarly, HHS is associated with total body potassium depletion due to lack of insulin and increased plasma osmolality [20,88]. The total-body potassium deficit has been estimated to be ~3–5 mEq/kg [87,100]. Insulin therapy lowers serum potassium levels by promoting the movement of potassium back into the intracellular compartment. Thus, potassium replacement should be started when the serum concentration is < 5.2 mEq/L to maintain a level of 4–5 mEq/L. The administration of 20–30 mEq of potassium per liter of fluids is sufficient for most patients; however, lower doses are required for patients with acute or chronic renal failure. Among patients with admission hypokalemia, with serum potassium levels < 3.3 mEq/L, insulin administration may result in severe symptomatic hypokalemia with muscle weakness and increased risk of cardiac arrhythmias. In such patients, potassium replacement should begin at a rate of 10–20 mEq/h and insulin therapy should be delayed until the potassium level rises above 3.3 mEq/L.

Bicarbonate

Routine administration of bicarbonate has not been shown to improve clinical outcomes such as time to resolution, length of hospital stay, or mortality in patients with DKA [101–104] and is generally only recommended in patients with life threatening acidosis with pH <6.9. Bicarbonate therapy may increase the risk of hypokalemia and cerebral edema [105,106]. Although no studies have looked at the effect of bicarbonate therapy in patients with severe acidosis, because of the potential risk of reduced cardiac contractility and arrhythmias, clinical guidelines recommend the administration of 50–100 mmol of sodium bicarbonate as an isotonic solution (in 400 mL of water) until pH is > 6.9. In patients with mild DKA with pH >7.0 or with HHS, bicarbonate therapy is not indicated.

Insulin regimens

Insulin administration is the mainstay of DKA therapy as it lowers the serum glucose by inhibiting endogenous glucose production and increasing peripheral utilization. Insulin also inhibits lipolysis, ketogenesis, and glucagon secretion, thereby decreasing the production of ketoacidosis.

Continuous IV infusion of regular insulin is the treatment of choice. Most treatment protocols recommend the administration of 0.1 unit/kg body weight bolus followed by continuous insulin infusion at 0.1 u/kg/hr until blood glucose is ~ 200 mg/dL (Figure 2). At this point, the dose is reduced by half (0.05 u/kg/hr) and rate is adjusted between 0.02–0.05 u/kg/hr, along with the addition of 5% dextrose, to maintain glucose concentrations between 140 and 200 mg/dL until resolution of ketoacidosis [1].

Several studies have demonstrated that the administration of subcutaneous doses of rapid-insulin analogs (lispro and aspart) every 1–2 hours is an effective alternative to the IV infusion of regular insulin in terms of time to resolution of DKA [107–109]. Patients are treated with an initial bolus of 0.2 – 0.3 U/kg followed by 0.1 – 0.2 U/kg every 1– 2 hours, respectively until glucose is < 250 mg/dl. The dose is then reduced by half to 0.05 U/kg every 1 hour or 0.01 U/kg every two hours until resolution of DKA [91,107]. Using scheduled subcutaneous insulin allows for safe and effective treatment in the emergency room and step-down units without the need for ICU care. The use of intramuscular injections of rapid-acting insulin is also effective in the treatment of DKA, but this route tends to be more painful than subcutaneous injection and might increase the risk of bleeding among patients receiving anticoagulation therapy [99,110]. It is important to keep in mind that the use of rapid-acting subcutaneous insulin analogues is not recommended for patients with arterial hypotension, severe and complicated DKA, or with HHS.

Transition to maintenance insulin regimen

Resolution of DKA is defined when glucose levels are lower than 250 mg/dl, venous pH > 7.30, normal anion gap, and serum bicarbonate ≥18 mEq/L [1]. HHS resolution is achieved when effective serum osmolality < 310 mOsm/kg, glucose level ≤ 250 mg/dL (13.8 mmol/l) in a patient who has recovered mental alertness and regaining of mental status [1,99].

Because of the short half-life of insulin (< 10 minutes) [111], abrupt cessation of the insulin may result is rebound hyperglycemia, ketogenesis, and recurrent metabolic acidosis. Subcutaneous basal insulin (NPH, glargine, detemir, degludec), should be given at least 2 hours before discontinuing the IV insulin infusion [1]. Earlier initiation 3–4 hours before discontinuation of insulin drip should be considered when using basal insulin analogs (glargine, determir, degludec), which have a longer delay in onset of action than NPH insulin. One randomized controlled trial evaluated the effect of co-administration of IV insulin with subcutaneous glargine shortly after the onset of treatment of DKA compared to IV insulin alone [112]. Patients who received glargine had slightly shorter time to resolution of DKA (based on closure of anion gap) and shorter hospital stay; however, these differences were not statistically significant [112]. Another study found that the administration of glargine

early in the course of treatment reduced the frequency of rebound hyperglycemia after transition off of insulin drip [113].

For insulin naïve patients, a starting total daily insulin dose of 0.5–0.6 units/kg may be started (half as basal and half as bolus) [1]. Patients with poor oral intake should receive basal insulin alone or, alternatively, may be continued on insulin drip until they are able to eat. Patients with known diabetes can be restarted on their previous insulin regimens, however an adjustment of the previous regimen should be considered if there is a history of frequent hypoglycemia, or significantly uncontrolled hyperglycemia before admission, as indicated by admission HbA1c. Multi-dose insulin regimens with basal insulin and prandial rapid-acting insulin analogs are the preferred insulin regimen for patients with T1D and DKA, and for most patients with HHS. A randomized controlled trial in DKA patients compared transition regimens of NPH and regular insulin twice daily versus glargine once daily and glulisine before meals found similar glycemic control between the two groups; however, the NPH/regular insulin group had more than double the rate of hypoglycemia (< 70 mg/dl) compared to the glargine/glulisine group [114].

Complications

Hypoglycemia is the most common complication during treatment, reported in 5–25% of patients with DKA [1,4,107]. Lack of frequent monitoring, and the failure to reduce insulin infusion rate and/or to use dextrose-containing solutions when blood glucose levels are < 200 mg/dL are the most important risk factors associated with hypoglycemia during insulin treatment. Many patients with hypoglycemia do not experience adrenergic manifestations of sweating, nervousness, fatigue, hunger and tachycardia, thus frequent blood glucose monitoring every 1–2 hours is mandatory [99]. Acute adverse outcomes of hypoglycemia include seizures, arrhythmias and cardiovascular events. Clinicians should be aware that recurrent episodes of hypoglycemia might be associated with a state of hypoglycemia unawareness (loss of perception of warning symptoms of developing hypoglycemia), which may complicate diabetes management after resolution of hyperglycemic crises.

Hypokalemia is the second most common complication during DKA and HHS treatment [4]. Although the admission serum potassium concentration is commonly elevated, during insulin treatment, plasma concentration of potassium will invariably decrease due increased cellular potassium uptake in peripheral tissues [1]. Thus, to prevent hypokalemia, replacement with IV potassium when concentration is < 5.2 mEq/l is indicated. In patients admitted with reduced serum potassium < 3.3 mEq/L, IV potassium replacement should begin immediately and insulin therapy should be held until serum potassium is ≥ 3.3 mEq/L to avoid severe hypokalemia.

Cerebral edema is rare in adults, but is reported in ~1 percent of children with DKA with a mortality rate between 20–40% [105,115]. The pathogenesis of cerebral edema is incompletely understood. Evidence for disruption of the blood–brain barrier has been found in cases of fatal cerebral edema [105,116]. The degree of edema formation during DKA in children correlates with the degree of dehydration and hyperventilation at presentation, but it does not correlate with initial osmolality, osmotic changes during treatment, or rate of fluid or sodium

administration [117]. Clinically significant cerebral edema usually develops 4–12 h after treatment has started, but it can occur as late as 24–48 h after the start of treatment. Clinical criteria includes altered mentation or fluctuating level of consciousness, abnormal motor or verbal response to pain, decorticate or decerebrate posturing, cranial nerve palsy (especially III, IV, and VI), abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne–Stokes respiration. Recommended treatment includes the administration of mannitol 0.5–1 g/kg IV over 20 min and repeat if there is no initial response in 30 min [118,119]. Hypertonic saline (3%), 5–10 mL/kg over 30 min, may be an alternative to mannitol, especially if there is no initial response to mannitol [120]. After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (≈10% of cases), especially thrombosis and cerebral infarction, hemorrhage, or dural sinus thrombosis, which may benefit from specific therapy [115,121–123]. Corticosteroid and diuretic therapy are of no proven benefits on the treatment of cerebral edema in DKA patients [124].

Rhabdomyolysis may occur in patients with DKA and more commonly with HHS resulting in increased risk of acute kidney failure. The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine, and monitoring creatine kinase concentrations every 2 to 3 h is recommended for early detection.

Prevention

Medication non-compliance is a leading cause of diabetic ketoacidosis among both newly diagnosed and recurrent episodes of DKA [39–41]. The mean cost of hospitalization is about $7,500 [40]. In half of such episodes, patients report inability to afford medication or to pay for transportation as the reason why medication was discontinued [41]. Development of system wide changes such as assistance programs to provide insulin to patients and reduce lapses in treatment may be a cost-effective way to reduce the rate of hospitalization for hyperglycemic emergencies. This could include implementation of safety nets such as assistance programs to provide insulin to patients and reduce lapses in treatment.

Multidisciplinary approaches with the use of clinical diabetes educators in close contact with and easily accessible to the patients has been shown to reduce the number of hospitalizations related to hyperglycemic emergencies [125]. Systems-based methods to reduce preventable causes of hyperglycemic emergencies may represent an important next step in reducing costs and improving patient care.

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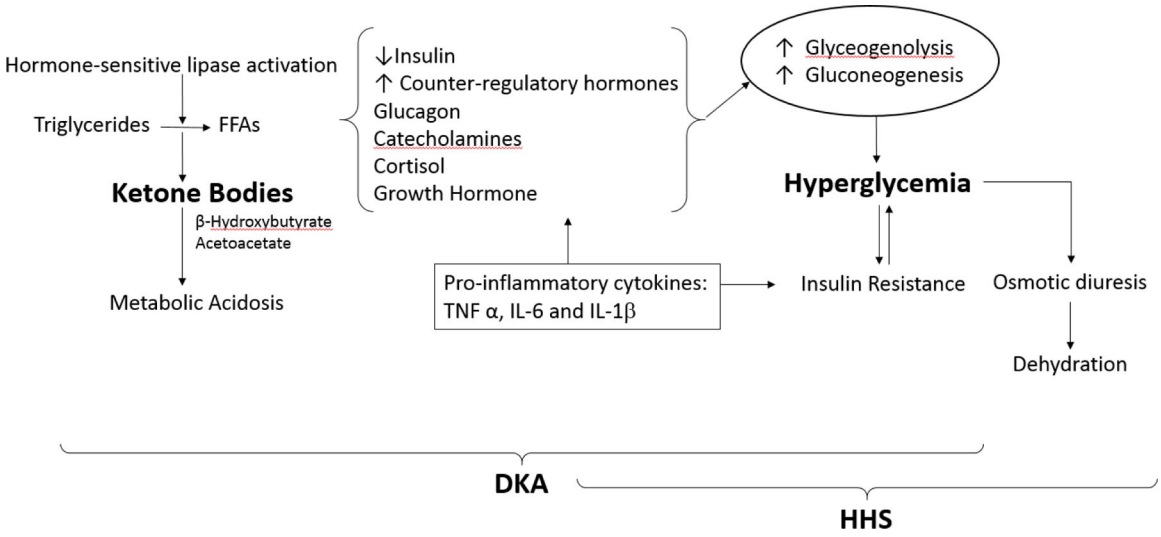

Figure 1.

Pathogenesis of Hyperglycemic Emergencies

Hyperglycemia and accumulation of ketones bodies result from a relative or absolute insulin deficiency and excess counter-regulatory hormones (glucagon, cortisol, catecholamines, and growth hormone).

Increased Ketone Bodies and ketoacidosis. Decrease in insulin levels combined with increased in counter-regulatory hormones, particularly epinephrine causes the activation of hormone sensitive lipase in adipose tissue and breakdown of triglyceride into glycerol and free fatty acids (FFAs). In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon. The two major ketone bodies are β-hydroxybutyrate and acetoacetic acid. Accumulation of ketone bodies leads to a decrease in serum bicarbonate concentration and metabolic acidosis. Higher insulin levels present in HHS inhibit ketogenesis and limit metabolic acidosis.

Increased Glucose Production in DKA and HHS. When insulin is deficient, hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. Hyperglycemia cause osmotic diuresis that lead to hypovolemia, decreased glomerular filtration rate and worsening hyperglycemia.

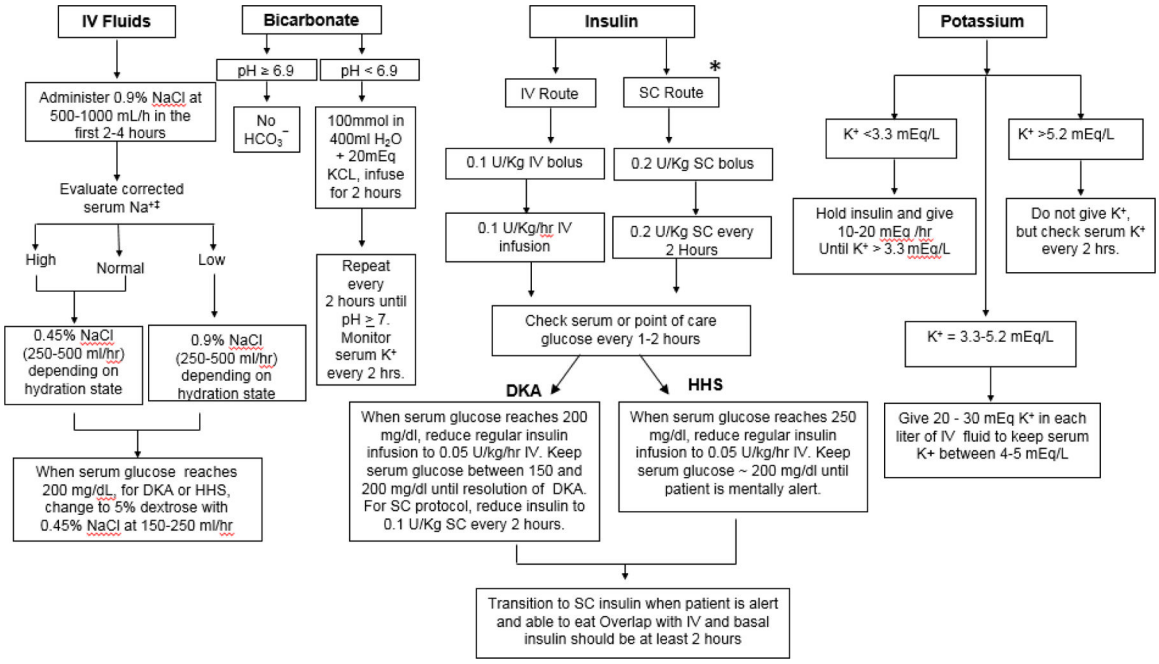

Figure 2.

Management of Hyperglycemic Emergencies

*Subcutaneous Insulin Protocol has not been validated for HHS

Modified by permission of Diabetes Care from the American Diabetes Association Consensus Statement on Hyperglycemic Crises, 2009 [1].

Table1:

Precipitating causes of Diabetic Ketoacidosis by Country.

Precipitating Causes, %	Australia	Brazil	China	Indonesia	Korea	Nigeria	Spain	Syria	Taiwan	USA
Newly diagnosed diabetes mellitus	5.7	12.2	NR	3.3	NR	NR	12.8	NR	18.2	17.2–23.8
Infection	28.6	25.0	39.2	58.3	25.3	32.5	33.2	47.8	31.7	14.0–16.0
Poor adherence to treatment	40.0	39.0	24.0	13.3	32.7	27.5	30.7	23.5	27.7	41.0–59.6
Other	25.7	15.0	10.9	17.1	11.2	4.8	23.3	7.8	6.2	9.7–18.0
Unknown	NA	8.8	25.9	8.0	30.8	34.6	NA	20.9	16.2	3.0–4.2

NA: Not Applicable

NR: Not Reported

Modified by permission of Nature Reviews: Endocrinology [99].

Table 2:

Clinical Features of Hyperglycemic Emergencies

Condition	Symptoms	Signs	Presentation
DKA	Polydipsia	Hypothermia	Acute onset (hours-days)
	Polyuria	Tachycardia	More common in T1D than T2D
	Weakness	Tachypnea	
	Weight loss	Kussmaul breathing	
	Nausea	Ileus	
	Vomiting	Acetone breath	
	Abdominal pain	Altered sensorium	
HHS	Polydipsia	Hypothermia	Insidious onset (days-weeks)
	Polyuria	Hypotension	Older age
	Weakness	Tachycardia	More common in T2D than T1D
	Weight loss	Altered sensorium	

Table 3:

Diagnostic Criteria for DKA and HHS

Measure	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10 to < 15	< 10	>18
Urine or Serum Ketones *	Positive	Positive	Positive	Small
Urine or Serum β-hydroxybutyrate (mmol/L)	>3.0	>3.0	>3.0	<3.0
Effective serum osmolality †	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental Status	Alert	Alert/drowsy	Stupor/coma	Stupor/Coma

* Nitroprusside reaction

† Effective serum osmolality: 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18

Modified by permission of Diabetes Care from the American Diabetes Association Consensus Statement on Hyperglycemic Crises, 2009 [1].