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HYPERGLYCEMIC CRISES

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ABSTRACT

Hyperglycemic emergencies, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS), are life-threatening complications requiring urgent treatment. DKA is more common in type 1 diabetes and results from absolute insulin deficiency, leading to hyperglycemia, dehydration, ketonemia and metabolic acidosis. Symptoms include polyuria, polydipsia, nausea, vomiting, and altered mental status. HHS is typically seen in type 2 diabetes and is defined by extreme hyperglycemia, severe dehydration, and hyperosmolarity without significant ketoacidosis. It often presents with confusion and neurological symptoms. Diagnosis of these conditions relies on blood glucose and ketone levels, blood gas, and electrolyte measurements. Fluid resuscitation, insulin therapy, and electrolyte correction are the mainstays of treatment. In HHS, intravenous insulin is used more cautiously to prevent rapid osmolar shifts and cerebral edema. Treatment protocols slightly differ in pregnancy, euglycemic ketoacidosis, and advanced kidney disease. Preventative strategies include education on sick day rules, regular clinic follow-ups in high-risk groups, and adherence to insulin therapy.

INTRODUCTION

Diabetes mellitus (DM) affects approximately 828 million people and its prevalence is expected to further grow in the coming years (1). It's estimated that 193 million people are asymptomatic and remain undiagnosed. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are acute life-threatening emergencies resulting from severe metabolic decompensation. DKA more commonly affects individuals with type 1 diabetes (T1DM) and is characterized by insulin deficiency and the triad of hyperglycemia, ketonemia and/or ketonuria, and metabolic acidosis, whereas HHS primary affects people with type 2 diabetes (T2DM) and presents with severe hyperglycemia, hyperosmolality, and severe dehydration.

Epidemiologic studies conducted in the U.S. and Europe over the past decade have revealed a concerning rise in the rate of hyperglycemic emergencies in adults with both T1DM and T2DM despite the previously noted reduction between 2000 and 2009 (2) (3) (4). The reported incidence of DKA in adults with T1DM varies across Europe, the U.S., and Israel, ranging from 0 to 56 events per 1,000 person-years. However, a study conducted in China between 2010 and 2012 reported a significantly higher rate of

263 per 1,000 person-years (5). In developing countries, DKA episodes affect 3.8%-73.4% of the diabetes population (6).

In the US, 240,000 patients had a primary diagnosis of DKA in 2020, corresponding to 10.2 cases per 1000 admissions and 27,000 had a diagnosis of HHS (1.2 cases per 1000 admissions), a significant rise in DKA cases compared to the total of 184,255 and 27,532 events for DKA and HHS respectively in 2014 (4). The cost of inpatient care for DKA in USA rose to $5.1 billion in 2014 and $6.76 billion in 2017, with the average cost per DKA admission increasing to approximately $31,000 (7) (8).

HHS is less common and is estimated to account for less than 1% of hospital admissions of patients with diabetes (9). Despite its rarity, HHS is associated with a higher mortality rate, ranging from 10% to 20%, which is about ten times higher than DKA. About 2/3 of adults admitted with DKA have T1DM, while almost 90% of the HHS patients have a known diagnosis of T2DM (3).

PATHOGENESIS

The primary distinction between DKA and HHS lies in the degree of insulin insufficiency. DKA results from severe insulin deficiency in the presence of increased counterregulatory hormones, including glucagon, cortisol, epinephrine, and growth hormone, which in turn leads to increased gluconeogenesis, accelerated glycogenolysis, and impaired peripheral glucose uptake. The combination of insulin deficiency and heightened counterregulatory hormone activity enhances lipolysis resulting in high release of free fatty acids from the adipose tissue (10). Free fatty acids are oxidized in the liver, leading to increased ketone production, ketonemia, and metabolic acidosis (11).

In HHS, there is relative insulin deficiency and residual insulin is enough to suppress lipolysis and prevent ketogenesis, but inadequate to regulate hyperglycemia. This persistent hyperglycemia is further enhanced by increased gluconeogenesis and decreased peripheral glucose uptake. Severe hyperglycemia leads to osmotic diuresis and subsequently to volume depletion. Increased thirst is often not sufficient to compensate for these losses and as a result osmolality rises, renal filtration declines, and as HHS progresses, severe dehydration ensues, frequently followed by cognitive impairment (12) (13).

Hyperglycemia in hyperglycemic crises is linked to a severe inflammatory state, marked by increased levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukins-1, -6, and -8, C-reactive protein, reactive oxygen species, and lipid peroxidation biomarkers, even in the absence of apparent infection or an acute cardiovascular event (13).

PRECIPITATING FACTORS

Most admissions for DKA/HHS are precipitated by one of the following risk factors (9) (14):

1. Infection: The stress of the infection can exacerbate the effects of the insulin deficiency by a rise in counterregulatory hormone levels and cytokines. In T1DM cohorts, infection accounts for up to 79.4% of the cases. Similarly, infection is a trigger factor for HHS in about 40-60% of cases.
2. Inadequate insulin dose or poor adherence to treatment: Lack of insulin due to omission or suboptimal treatment regimens is one of the most common precipitants of DKA and HHS.
3. New diagnosis of diabetes: DKA can be the initial clinical presentation of T1DM. In recent years, more people with undiagnosed T2DM diabetes present with DKA or mixed DKA/HHS; part of these cohorts are eventually diagnosed with ketosis prone diabetes (discussed in the special cases section).
4. Medical or surgical emergencies, such as myocardial infarction, stroke, or trauma, can be complicated by diabetes related emergencies.
5. Medications: Certain medications can impair glucose metabolism, increase gluconeogenesis and insulin resistance. Glucocorticoids can lead to significant hyperglycemia and subsequently DKA or

HHS. A rare complication of SGLT-2 inhibitors is euglycemic ketoacidosis that is further discussed below.

DIAGNOSTIC CRITERIA AND CLINICAL MANIFESTATIONS

Based on the recent global consensus, the following three criteria are used to establish the diagnosis of DKA (13):

1. Hyperglycemia ≥200 mg/dL (11.1 mmol/L) or a prior history of diabetes irrespective of the presenting glucose reading.
2. Elevated ketone body concentration: venous or capillary β-hydroxybutyrate ≥3.0 mmol/L or in the early stages of DKA urine ketone 2+ or greater.
3. Metabolic acidosis: pH<7.3 and/or bicarbonate concentration <18 mmol/L.

It's worth noting that urine ketone testing, which measures acetoacetate, may underestimate the level of ketonemia due to a lag in the formation of acetoacetate and overestimate it in the advanced stages of DKA due to the increased clearance of β-hydroxybutyrate and conversion to acetoacetate (10). Moreover, ketone tests based on the nitroprusside reaction can give false-positive results in the presence of drugs containing sulfhydryl groups (15, 16). Hence, measurement of venous or capillary β-hydroxybutyrate is recommended for the diagnosis. The use of bedside capillary ketone monitors is now advocated as the best standard of care.

The most common symptoms are nausea and vomiting and abdominal pain, which can mimic an acute abdomen. General symptoms include fatigue and malaise. Osmotic symptoms (polydipsia, polyuria) and unintentional weight loss often precede the diagnosis. Individuals can exhibit neurological symptoms including confusion, headache, lethargy, and coma. Kussmaul breathing (deep, labored breathing) occurs in 28% of cases (17). Fruity breath odor due to ketone production, another distinct sign of DKA, might be present. Tachycardia and hypotension due to dehydration are often present along with dry mucous membranes and decreased skin turgor.

Contrary to DKA, HHS is characterized by absence of severe ketonemia and metabolic acidosis. There are four diagnostic criteria as per global consensus (13).

1. Plasma glucose >600 mg/dL (33.3 mmol/L).
2. Hyperosmolality defined as effective osmolality >300 mOsm/kg or total serum osmolality > 320 mOsm/kg.
3. Absence of significant ketonemia: β-hydroxybutyrate <3.0 mmol/L or urine ketone < 2+.
4. Absence of acidosis: pH≥7.3 and bicarbonate concentration ≥ 15 mmol/L.

General symptoms include significant fatigue and weakness. Osmotic symptoms and weight loss often precede the acute presentation. Neurological symptoms, including confusion, focal neurological deficits, lethargy, seizures, and coma are more frequent in HHS. Signs of severe dehydration and volume depletion include tachycardia and severe hypotension as well as general signs of dehydration. When left untreated, it can lead to multiorgan failure and death (9).

The differences between DKA and HHS are shown in Table 1. Patients may manifest symptoms and laboratory studies of both DKA and HHS as DKA and HHS represent a spectrum of insulin deficiency disorders.

Table 1. DIFFERENCES BETWEEN DKA AND HHS		
Clinical / Laboratory feature	**DKA**	**HHS**
Onset	Rapid (hours to 1-2 days)	Gradual (several days to weeks)
Blood glucose	200-600 mg/dL (11.1-13.3 mmol/L)	>600 mg/dl (13.3 mmol/L)
Ketones	Ketonemia >3 mmol/L or ketonuria 2+ or higher	Absent or <3 mmol/L
pH (acidosis)	<7.3	≥7.3
Bicarbonate	<18 mmol/L	≥ 15 mmol/L
Osmolality	Moderately elevated	Severely elevated (>320 mOsm/kg)
Neurological symptoms	Mild to moderate confusion	Severe confusion, seizures, coma

Other Laboratory Findings

Leukocytosis is a common finding in patients with DKA or HHS and might be resulting from acute stress, but a white blood cell count > 25,000/μL may indicate an underlying infection and warrants further investigations (18). Hypertriglyceridemia is frequently seen in HHS and is nearly always present in DKA (19). Additionally, elevated amylase and lipase levels can be found in DKA (20).

In DKA, the anion gap, calculated as $[Na^+]$ - ($[Cl^-]$ + $[HCO_3^-]$), is typically elevated (>12 mEq/L), reflecting the progression of ketoacidosis. However, other factors such as nausea, vomiting, and renal losses can attenuate this rise by contributing to bicarbonate loss and deranged electrolytes. Moreover, Kussmaul breathing induces respiratory alkalosis, often resulting in a mixed metabolic and respiratory acid-base disturbance.

DIFFERENTIAL DIAGNOSIS

DKA must be differentiated from the following conditions:

1. Alcoholic Ketoacidosis: Like DKA, it's characterized by high anion gap metabolic acidosis but with normal or low glucose levels (21).
2. Starvation Ketoacidosis: Malnutrition or prolonged fasting can lead to ketosis and mild acidosis; however blood glucose levels are normal or low (22).
3. Lactic Acidosis: Often seen in sepsis and dehydration, it leads to metabolic acidosis in the absence of ketonemia. It's sometimes seen in individuals with impaired renal function and diabetes treated with metformin (10).
4. Toxins: Substances such as methanol and ethylene glycol can lead to high anion gap metabolic acidosis.
5. Renal Failure: Acute or chronic kidney disease is associated with metabolic acidosis and uremia, which can present with symptoms similar to those of DKA as discussed later (23).

Besides distinguishing HHS from DKA, several conditions can mimic or coexist with HHS (24).

1. Sepsis: Characterized by dehydration and altered mental status, sepsis can also act as a precipitating factor for HHS.

2. Stroke: When focal neurological deficits are present, HHS may be mistaken for stroke. Glucose testing is essential for an accurate diagnosis.
3. Uremia: Acute or chronic kidney disease can cause altered mental status, but in the absence of diabetes, blood glucose levels tend to remain normal.
4. Electrolyte disorders: Hyponatremia or hypernatremia can lead to confusion and neurological symptoms including seizures, lethargy, and coma. Presence of hyperosmolality and hyperglycemia along with electrolyte disorders can unmask an underlying hyperglycemic crisis.

COMPLICATIONS

1. Hypoglycemia: One of the most common complications of treatment especially in patients with DKA (25).
2. Hypokalemia: Due to intracellular shift of potassium following insulin treatment, hypokalemia is often seen during treatment of hyperglycemic emergencies. It's estimated to affect about 55% of DKA and 51% of HHS patients (25).
3. Hyperchloremic Non–Anion Gap Acidosis: This transient and typically self-resolving condition can result from excessive normal saline infusion or the metabolism of ketoanions to bicarbonate during DKA resolution (26) (27).
4. Cerebral Edema: This complication is more common in DKA, particularly in younger patients, but has also been reported in HHS. A declining level of consciousness, lethargy, and headache should raise suspicion. If untreated, it can progress to seizures, pupillary abnormalities, bradycardia, and respiratory arrest, with a high risk of mortality and permanent neurological damage. The exact cause remains unclear but may involve osmotic shifts, hypoperfusion, and inflammatory processes (10) (28).
5. Hypoxemia and rarely non-cardiogenic pulmonary edema: It may be associated with a decrease in the colloid osmotic pressure leading to pulmonary edema.
6. Thrombosis: Both DKA and HHS are prothrombotic states (29) (30). The risk is higher in HHS potentially due to the concurrent hypernatremia or raised vasopressin concentrations, which are considered thrombogenic. Hyperglycemia is also linked to a pro-inflammatory effect on the endothelium. An individual risk assessment for venous thromboembolism (VTE) should be performed for all patients presenting with DKA or HHS to decide if prophylactic or therapeutic dose of anticoagulation should be prescribed (31) (9). Given limited clinical trial data, therapeutic anticoagulation dose in all patients presenting with HHS is not recommended.
7. Acute kidney failure: A common complication of DKA and HHS, usually resulting from severe dehydration due to osmotic diuresis.

TREATMENT

Fluids

Administration of intravenous (IV) fluids restores circulating intravascular volume and thus organ perfusion, facilitating the excretion of glucose and ketone bodies. Additionally, it improves insulin sensitivity by reducing the effect of counterregulatory hormones. Isotonic fluids have been the preferred choice for over 50 years. Normal saline 0.9% has been the standard fluid; however, concerns have been raised about its potential to cause hyperchloremic metabolic acidosis, particularly when administered in large volumes. Recent prospective and observational studies, as well as meta-analyses, have shown that using balanced crystalloid solutions such as Ringer's lactate leads to faster resolution of DKA, shorter hospital stays, and lower incidence of hyperchloremic metabolic acidosis (32) (33, 34).

In DKA, an infusion of 15-20 ml per Kg body weight within the first hour is usually appropriate in adults without renal or cardiac compromise (35). As a general rule, administration of isotonic saline or crystalloid solutions at a rate of 500–1,000 mL/h during the first 2–4 hours is recommended (13). Once intravascular volume is repleted, fluid replacement rate and choice of fluid are guided by vital signs, fluid

balance, and serum electrolyte levels (8) .In hypernatremia, isotonic solutions are still the preferred choice due to lower risk of rapid correction of sodium levels and cerebral edema (36). Fluid replacement should restore estimated deficits within the first 24–48 h. Rapid replacement might not be appropriate in individuals with chronic cardiac failure, chronic kidney disease (CKD), frailty, and older age. If there are concerns about hyperchloremic metabolic acidosis, Ringer's lactate solution can be used instead. When plasma glucose falls below 250 mg/dL (13.9 mmol/L), 5–10% dextrose in addition to the 0.9% sodium chloride is suggested to prevent hypoglycemia while insulin is used to correct ketonemia.

In HHS, the goal of treatment is to replace approximately 50% of the fluid deficit within the first 12 h and the remainder in the following 12 h. Similarly to DKA, initial administration rate of isotonic saline is 500–1,000 mL/h during the first 2–4 h. Fluid replacement alone leads to reduction in glucose levels which in turn decreases serum osmolality due to the water shift into the intracellular space. This results in increasing sodium levels, but this is not necessarily an indication for hypotonic solutions unless the osmolality is not adequately decreasing. If the rise in serum sodium is much greater than 2.4 mmol/L for every 5.5 mmol/L fall in blood glucose, this suggests inadequate fluid replacement and requires a higher infusion rate (37). If fluid replacement is adequate but glucose and osmolality are not falling at the desired rate, then 0.45% sodium chloride solution should be considered. Overall, the goals of treatment are a decrease in osmolality between 3 and 8 mOsmol/kg per hour, a sodium reduction by no more than 10 mmol/L in 24 hours, and hourly glucose fall by up to 5mmol/L (37).

Insulin

Insulin therapy is the mainstay of DKA treatment and should be started immediately after the diagnosis using a fixed-rate intravenous insulin infusion started at 0.1 units/kg/h. Short-acting insulin is the preferred choice. An insulin bolus (0.1 units/kg/hour) given intravenously or intramuscularly is suggested in some treatment protocols if a delay in obtaining venous access is expected, followed by the fixed rate infusion (13) (38). When blood glucose falls below 250 mg/dL (13.9 mmol/L), the rate should be halved to 0.05 units/kg/h. Subsequently, the infusion continues until the ketoacidosis is resolved and rate adjustments are made depending on the glucose levels with a target glucose of 200 mg/dl (11.1 mmol/l) (13).

For patients on long-acting insulin before admission, basal insulin can be continued during the administration of the IV insulin infusion, which will later enable the transition to a subcutaneous basal bolus regimen (39). In the newly diagnosed patients, basal insulin is initiated at 0.15–0.3 units/kg. Once DKA has resolved and oral intake is adequate, IV insulin can be discontinued, and rapid acting insulin is resumed with meals or initiated in the newly diagnosed. For patients who hadn't been on simultaneous IV insulin and SC basal insulin during treatment, the infusion should be stopped at least 1-2 hours after the administration of SC insulin. If oral intake is poor, transition to variable rate insulin infusion along with glucose solutions is recommended. Criteria for resolution of DKA include (40):

1. Blood glucose< 200 mg/dl (11.1 mmol/l)
2. Venous pH > 7.3 and / or bicarbonate ≥18 mmol/L
3. Plasma ketone <0.6 mmol/L

The anion gap is no longer used as a criterion, as it may also be elevated in hyperchloremic metabolic acidosis.

In HHS, mild or moderate ketonemia (blood β-hydroxybutyrate ≥1.0 to <3.0 mmol/L or urine ketones <2+) in the absence of acidosis (pH ≥7.3 and bicarbonate ≥18 mmol/L) is treated with IV fluids and a fixed-rate IV insulin infusion is only started once the glucose stops falling; this is to prevent large osmotic shifts and subsequently neurological complications (37). If insulin is required, the recommended initial rate is also more conservative at 0.05 units/kg/h.

Mixed DKA/HHS is defined as hyperosmolality (>320 mOsm/kg), β-hydroxybutyrate ≥3.0 mmol/L or ketonuria ≥2+ and presence of acidosis (pH <7.30, or bicarbonate <18 mmol/L) and has been reported in more than one-third of people with hyperglycemic crises (41). DKA and HHS share some common mechanisms in the underlying pathophysiology. In both conditions, counterregulatory hormones are elevated, while the release of cytokines leads to reduced response to insulin. It's possible that glucotoxicity, inflammation, and oxidative stress all lead to a relative insulin deficiency due to beta cell exhaustion resulting in this overlap (37, 42). Similarly to DKA, it requires higher doses of insulin (starting rate for fixed rate insulin infusion: 0.1 units/kg/h) and IV fluids with the goal to achieve a positive balance of 3–6 L during the first 12 h and the remaining replacement in the following 12 h, although complete resolution may take up to 72 h (37). Transition to SC insulin follows the same principles as DKA.

The criteria for the resolution of HHS has recently been agreed such that overall serum osmolality (total and effective) should fall below 300 mOsm/kg, blood glucose below 250 mg/dL (13.9 mmol/L), urine output is above 0.5 mL/kg/h, and cognitive status has improved (43).

Bicarbonate

Bicarbonate is not routinely administered since IV fluids and insulin usually suffice to correct the metabolic acidosis of DKA (34). Higher risk of hypokalemia, cerebral edema, and development of paradoxical central nervous system acidosis have been reported with bicarbonate treatment (10, 40) and therefore their use is limited in severe metabolic acidosis (i.e., pH <7.0). In this case, 100 mmol of sodium bicarbonate (8.4% solution) in 400 mL of an isotonic solution can be administered every 2 h to achieve a pH >7.0 (43).

Potassium

Total body potassium is reduced in DKA/HHS due to renal losses resulting from osmotic diuresis, extrarenal losses due to vomiting, and concurrent hyperaldosteronism, however this reduction is often masked by the potassium movement from the intracellular to the extracellular space due to the lack of insulin and presence of acidosis. A further reduction results from treatment with insulin that increases uptake of potassium by cells and fluids that restore the intravascular volume and metabolic balance leading to increased potassium excretion in the urine (44). Potassium replacement should be started when serum levels are below 5.5 mmol/L with a target range of 4–5 mmol/L. This is usually achieved with 20–30 mmol of potassium in each liter of intravenous solution. Potassium levels below 3.5 mmol/L require a higher rate of 10 mmol/h and insulin therapy should be deferred until the potassium level is above 3.5 mmol/L to reduce risk of lethal arrhythmias and respiratory muscle weakness (45).

Phosphate

Hypophosphatemia can result from the osmotic shift into the extracellular fluid and the renal losses due to osmotic diuresis. Replacement is indicated in the presence of muscle weakness or respiratory / cardiac distress and phosphate levels below 1.0 mmol/L. In this case 20–30 mmol of potassium phosphate is added to the replacement fluids.

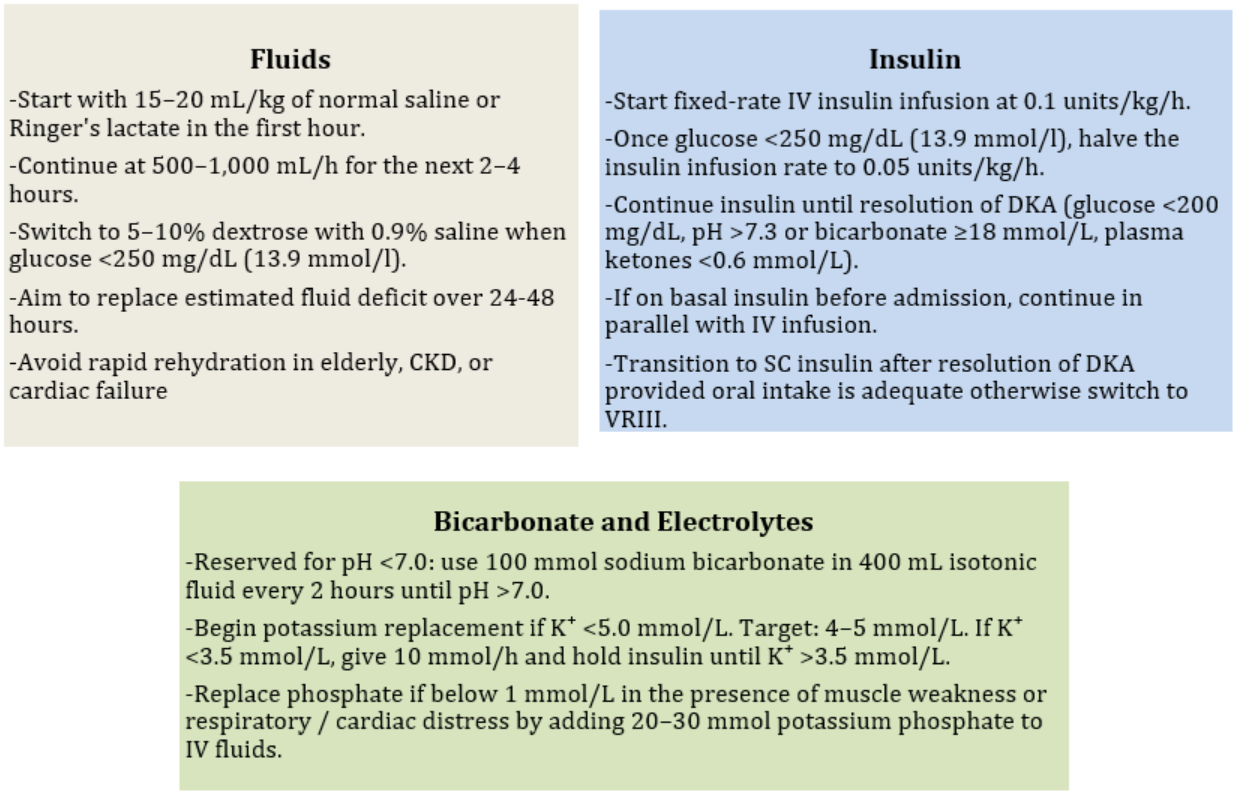

Figure 1. Key points for the management of DKA.

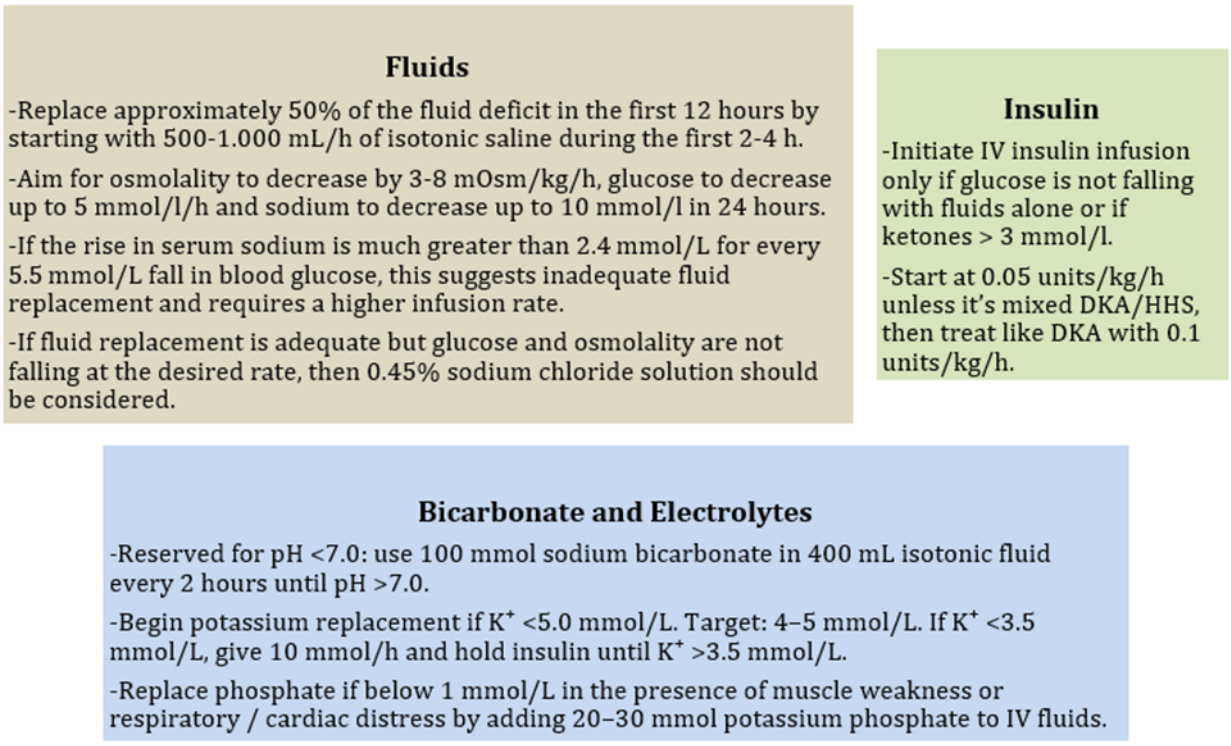

Figure 2. Key points for the management of HHS.

SPECIAL SITUATIONS

Pregnancy

DKA is rare in pregnancy and has an estimated incidence of 0.5–3% with up to 30% being euglycemic DKA (glucose less than 13.9 mmol/l) (46). Fetal demise rates remain as high as 35% for a single episode of DKA despite substantial improvements in perinatal and neonatal care (47). DKA most commonly presents in the third trimester and in women with T1DM followed by gestational diabetes (48). Since euglycemic DKA can present in one third of the cases, increased awareness and low threshold for ketone testing is required when women present with nausea, vomiting, abdominal pain, or recent osmotic symptoms.

During pregnancy, insulin resistance progressively increases to ensure adequate fetal nutrition, while insulin secretion rises to meet these higher demands. Additionally, pregnancy is a ketogenic state characterized by increased lipolysis and ketogenesis, driven by relative maternal starvation and hypoglycemia (49). This explains why DKA can develop in response to triggers such as insulin omission, steroid use, or infection.

Hyperosmolar hyperglycemic state (HHS) is rare in pregnancy due to physiological adaptations, including an 8–10 mmol/kg reduction in maternal plasma osmolality and a lower threshold for vasopressin secretion, both of which reduce the risk of hyperosmolality. However, as insulin resistance increases throughout gestation, HHS is more likely to occur in women with type 2 diabetes mellitus (T2DM) (50).

Diabetic emergencies in pregnancy should be managed in level 2 critical care units such as HDU or ICU. Differences in the management of DKA in pregnancy include the need for fetal monitoring with frequent cardiotocography (CTGs) and in some cases ultrasounds and potentially a more conservative approach in the fluid resuscitation that should be guided by frequent assessment of the hemodynamic status (51). Isotonic saline (0.9%) remains the fluid of choice and should be administered in boluses of 500 ml over 10-15 min if the SBP is less than 90 mmHg and repeated if SBP remains below target. Following initial resuscitation, maintenance fluids can be prescribed as per adult guideline for management of DKA with a recommended rate of 5-15 ml/kg/hour. When it comes to insulin administration, current weight should be considered to determine the infusion rate. Once DKA is resolved, stricter glycemic control should be promptly achieved based on current recommended targets (fasting glucose <5.3 mmol/l, 1 hour post meals< 7.8 mmol/l).

Diabetic ketoacidosis (DKA) can lead to fetal cardiac arrhythmias and, in up to one-third of cases, fetal demise (52). Fetal heart rhythm often normalizes after correction of maternal metabolic acidosis, though this may take 4–8 hours (51). The decision for urgent delivery should be individualized, taking into account gestational age and response to therapy (46).

As noted, euglycemic DKA (euDKA) is common in pregnancy. This is attributed to increased fetal glucose utilization via enhanced placental glucose transporter expression, increased renal glucose excretion due to higher glomerular filtration, and hemodilution from expanded plasma volume. The treatment of euDKA differs from standard DKA management, requiring early initiation of 5% dextrose alongside normal saline via a separate line.

In HHS, weight measurement can assist with fluid replacement. A loss of weight more than 10% of the last clinic weight measurement indicates severe volume depletion and fetal risk (50). Despite stricter glucose targets during gestation, osmolality reduction should not exceed the recommended rate due to risk of cerebral edema.

Recurrent DKA

Recurrent episodes of DKA occur more frequently in females, young age groups, ethnic minorities, and individuals with suboptimal glycemic control (HbA1c > 86 mmol/mol). The most frequent trigger is insulin omission (53). This is often driven by psychosocial factors, including difficulty accepting a chronic condition, depression, eating disorders, fear of weight gain, and severe anxiety about hypoglycemia (54-56). Low socioeconomic status and substance abuse have also been identified as risk factors.

Family conflict and a lack of parental involvement in diabetes management also contribute, particularly in adolescents (57). An observational retrospective case control study showed that 75% of all patients with recurrent DKA did not attend at least one appointment within the previous 12 months; patients had a mean age of 31 years reinforcing the younger age distribution of recurrent DKA cases (58). Data from 6 institutions in Chicago showed a prevalence of recurrent DKA at 21.6% with 5.8% of the cohort presenting with 4 or more episodes. Individuals with fragmented care in different healthcare institutions were at higher risk of recurrence and were more commonly of African American/Black ethnicity (59).

Preventing further episodes of DKA is the primary goal in this high-risk population. Strategies include insulin administration by family members or community nurses, structured insulin regimens, and hybrid closed-loop systems when there are no concerns about technology use. Ongoing support from a diabetes specialist psychologist and programs for complex cases, such as fear of hypoglycemia or eating disorders, are also important. Additionally, virtual appointments can provide flexibility and reduce missed appointments, while technology-based communication, such as messaging, can facilitate frequent contact with the diabetes care team.

Ketosis Prone Diabetes

Ketosis prone diabetes is a distinct variant form that has been described in recent decades, in which patients present with DKA without the underlying autoimmunity of T1DM (GAD and anti-islet cell antibody negative). The genetic aspect remains under investigation with contradictory results so far. It most frequently presents in African, Asian and Indian and Hispanic populations. It's estimated that it accounts for 25% to 50% of African Americans and Hispanics with a new diagnosis of DKA (60). However, the overall prevalence remains unknown. It's also more common in middle aged individuals, males, and overweight or obese people (61).

One of the unique aspects of this entity is the reversibility with high chance of insulin cessation and diabetes remission. This usually occurs after several months of insulin therapy and lifestyle interventions with only one fourth of patients remaining insulin dependent (62). Recurrent DKA is rare, and the clinical course generally resembles that of T2DM with oral agents such as metformin often being an effective treatment.

Ketoacidosis stems from the lack of beta cell insulin secretion on the background of severe hyperglycemia. There is often no preceding trigger factor. Patients may report osmotic symptoms prior to DKA presentation. The mechanism for the acute onset of severe hyperglycemia is currently unknown. Once normoglycemia is restored, glucose-stimulated insulin secretion starts to recover and maximizes approximately 12 weeks after the resolution of DKA and initiation of insulin treatment (63) (64). Improvement in c-peptide levels suggests temporary functional abnormalities of beta cells as opposed to permanent damage. Insulin sensitivity also remarkably improves following treatment.

Biochemical parameters during the acute presentation are consistent with the classic form of DKA. Management of DKA doesn't differ, however once patients are established on subcutaneous insulin, close monitoring is advised since requirements are expected to decrease in the following months (60).

Hyperglycemic Emergencies In Chronic Kidney Disease

DKA IN CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) remains a major complication of diabetes, with end-stage renal disease (ESRD) affecting up to 31.3% of cases (65). Declining kidney function leads to impaired gluconeogenesis and reduced insulin degradation, resulting in lower insulin requirements. However, despite these lower needs, individuals with advanced CKD can still develop DKA and, more rarely, HHS.

Water excretion is impaired and osmotic diuresis decreases, which is less pronounced in people with impaired renal function, and it is absent in those with anuria. On the contrary, polydipsia is still present due to hypertonicity leading to increased water intake, and subsequent expansion of interstitial and intravascular volume.

Chronic metabolic acidosis is common in advanced CKD due to decreased acid excretion and high endogenous and exogenous acid loads (66). Acidosis deteriorates rapidly with the accumulation of ketone bodies. Distinguishing between DKA and acidosis of uremia remains challenging as both share similar symptoms (67). Ketone measurements are therefore crucial for prompt diagnosis especially in the presence of markedly elevated anion gap (>20). The recommended diagnostic threshold remains a ß-hydroxybutyrate level of more than 3 mmol/L (68). The diagnostic criteria for DKA do not differ in individuals with CKD.

Clinical findings vary significantly depending on the stage of renal impairment. In individuals with adequate diuresis, volume status is often reduced, further exacerbated by extrarenal losses such as vomiting and diarrhea. In those with decreased diuresis or anuria, volume status may be expanded, leading to signs of fluid overload such as shortness of breath, raised jugular venous pressure, peripheral edema, hypertension, and pulmonary edema.

In patients on dialysis hyperglycemia can be corrected with hemodialysis, with studies reporting a 36% decrease in blood glucose levels two hours post-dialysis (69); hemodialysis also helps correct hyperkalemia and acidosis; however, ketogenesis may persist due to insufficient insulin. The timing of the latest dialysis session, the volume of fluid removed, the presence of extra renal or excessive insensible losses affects the above parameters making diagnosis even more challenging. For this reason, some authors suggest measuring capillary ketone and lactate levels in all people with ESRD and metabolic acidosis (63).

The management of DKA depends on the stage of CKD, which directly influences fluid balance and insulin requirements. In ESRD, insulin requirements are lower, so an initial infusion rate of 0.05 units/kg/hour is recommended instead of 1 unit/kg/hour. The insulin dose should be adjusted based on treatment response, aiming for blood glucose reduction of 3–5 mmol/L per hour, plasma ketone reduction of 0.5 mmol/L per hour, and serum bicarbonate increase of 3 mmol/L per hour. The reduction of effective osmolality should not exceed 8 mOsm/kg/hour to minimize the risk of cerebral osmotic demyelination.

If the initial assessment shows normal or increased volume status, intravenous fluids are not required unless there is hypotension or other signs of volume depletion. If fluid overload is present, insulin infusion alone may be sufficient. However, severe overload with pulmonary edema requires dialysis, and renal consultation is recommended. If volume status is unclear, central pressure monitoring can help guide management. If the patient is hypovolemic (GI losses, excessive insensible losses, dry mucous membranes, reduced skin turgor, hypotension, weight at or below their post-dialysis weight), fluid resuscitation with boluses of 250 ml of sodium chloride 0.9% with frequent monitoring of clinical and laboratory parameters is recommended. In individuals on dialysis, pre-dialysis weight should be targeted (67).

Serum electrolytes should be closely monitored with potassium supplementation reserved for patients with hypokalemia. Serum potassium levels are often elevated, and hyperkalemia tends to be more severe in people on dialysis for the same level of hyperglycemia. In either case, it is expected to improve with the administration of intravenous insulin (70). Continuous cardiac monitoring is recommended when potassium exceeds 5.5 mmol/L. Correction with 40 mmol/L of potassium chloride is recommended when serum potassium is below 3.5 mmol/l (71).

Emergency hemodialysis should be considered in major hyperglycemia, severe metabolic acidosis in anuric patients, significant hypertonicity with often co-existent severe hyponatremia, and persistent hyperkalemia that does not respond to insulin administration. Rapid correction of blood glucose levels and plasma osmolality should be avoided to reduce risk of cerebral edema (72). Use of bicarbonates is generally limited for severe metabolic acidosis (pH<6.9) (34). Since bicarbonate regeneration is insufficient in advanced CKD, their use can be considered when pH<7.2.

EUGLYCEMIC DKA IN ADVANCED CKD

Euglycemic ketosis can present during continuous renal replacement (CRRT) with glucose free solutions and low caloric intake. During CRRT, glucose is removed from the blood (from 30 to 160 g per day depending on glycemia and hemofiltration rate) and glycogen stores are depleted within 2-3 days when glucose free solutions are used (73). This leads to increased glucagon levels and enhances gluconeogenesis and ketogenesis, resulting in euglycemic ketoacidosis. It can present even in the absence of diabetes (74). A high anion gap metabolic acidosis in people on CRRT should raise suspicion and prompt ketone testing. Ketosis is managed by raising the daily caloric intake (some authors suggest 25 kcal/kg/day) with a supplemental dextrose infusion along with insulin administration. Glucose-containing CRRT solutions should also be considered (73).

HHS IN ADVANCED CKD

HHS is rare in people with advanced CKD, due to lack of significant diuresis, but a mixed HHS/DKA picture can be seen considering that glucose accumulates in the extracellular space leading to hypertonicity and significant hyperglycemia. Diagnostic criteria remain the same in advanced CKD, however since urea is often increased, effective osmolality is a more reliable marker for both diagnosis and assessing response to treatment (23).

Mixed DKA/HHS should be managed as DKA. There are no evidence-based recommendations on the management of HHS in people with advanced CKD. Aggressive fluid resuscitation (30 mL/kg crystalloid) is considered safe for dialysis-dependent patients in other settings, such as sepsis-induced hypotension, based on retrospective data (75) (76). Since people with HHS are usually significantly dehydrated, a similar initial approach with frequent reassessment of fluid responsiveness and volume status could be considered.

PREVENTION

Approximately one in five patients admitted for DKA will be readmitted within 30 days (77). Insulin omission and underlying infections are the most common precipitating factors. As mentioned before, psychological factors, low socioeconomic status, younger age, and substance abuse are often present in people with recurrent episodes of DKA. Identifying patients at risk is crucial to prevent diabetic emergencies; this can be achieved with more frequent clinic visits, structured education programs for example those designed for type 1 diabetes and disordered eating, additional support from the psychiatry service, access to continuous glucose monitoring, and when appropriate, use of hybrid closed loop systems. Funding of community programs targeting people who struggle to access medical care due to socioeconomic reasons should be encouraged especially if we consider the financial implications of diabetic emergencies and complications (78) (79).

Patient education on sick day rules is important for DKA prevention and should be discussed periodically. Temporary discontinuation of SGLT-2 inhibitors in acute illness or planned surgery, when oral intake of food and water is restricted, is recommended to reduce the risk of euglycemic ketoacidosis (80). Education of family members and school staff can help prevent or at least recognize promptly the symptoms of DKA in children and adolescents with type 1 diabetes. Likewise, close observation and early detection of symptoms can help prevent HHS in older adults (36).

SUMMARY

Hyperglycemic emergencies, including DKA and HHS, are serious, life-threatening complications and require increased prompt recognition and urgent medical intervention. DKA is more common in type 1 diabetes and results from absolute insulin deficiency, while HHS is typically seen in type 2 diabetes and is defined by extreme hyperglycemia, severe dehydration, and hyperosmolarity without significant ketoacidosis. The diagnosis of these conditions relies on blood glucose and ketone levels, blood gas, and electrolyte measurements. Treatment focuses on fluid resuscitation, insulin therapy, and electrolyte correction. In HHS, intravenous insulin is used more cautiously to prevent rapid osmolar shifts and cerebral edema. Treatment protocols may need to be adjusted in special populations, including pregnant women, people presenting with euglycemic ketoacidosis, or advanced kidney disease. Preventative strategies including education on sick day rules, regular clinic follow-ups in high-risk groups, and adherence to insulin therapy, are essential in reducing the incidence of these emergencies.

REFERENCES

1. Collaboration NCDRF. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. Lancet. 2024;404(10467):2077-93.
2. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in Hospital Admission for Diabetic Ketoacidosis in Adults With Type 1 and Type 2 Diabetes in England, 1998-2013: A Retrospective Cohort Study. Diabetes Care. 2018;41(9):1870-7.
3. Benoit SR, Hora I, Pasquel FJ, Gregg EW, Albright AL, Imperatore G. Trends in Emergency Department Visits and Inpatient Admissions for Hyperglycemic Crises in Adults With Diabetes in the U.S., 2006-2015. Diabetes Care. 2020;43(5):1057-64.
4. Leiva-Gea I, Fernandez CA, Cardona-Hernandez R, Lozano MF, Bahillo-Curieses P, Arroyo-Diez J, et al. Increased Presentation of Diabetic Ketoacidosis and Changes in Age and Month of Type 1 Diabetes at Onset during the COVID-19 Pandemic in Spain. J Clin Med. 2022;11(15).
5. Fazeli Farsani S, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA. Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. BMJ Open. 2017;7(7):e016587.
6. Haile HK, Fenta TG. Magnitude, risk factors and economic impacts of diabetic emergencies in developing countries: A systematic review. PLoS One. 2025;20(2):e0317653.
7. Ramphul K, Joynauth J. An Update on the Incidence and Burden of Diabetic Ketoacidosis in the U.S. Diabetes Care. 2020;43(12):e196-e7.
8. Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health Care Utilization and Burden of Diabetic Ketoacidosis in the U.S. Over the Past Decade: A Nationwide Analysis. Diabetes Care. 2018;41(8):1631-8.
9. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care. 2014;37(11):3124-31.
10. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers. 2020;6(1):40.
11. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care. 2001;24(1):131-53.
12. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinol Metab Clin North Am. 2000;29(4):683-705, V.
13. Umpierrez GE, Davis GM, ElSayed NA, Fadini GP, Galindo RJ, Hirsch IB, et al. Hyperglycemic Crises in Adults With Diabetes: A Consensus Report. Diabetes Care. 2024;47(8):1257-75.

14. Ahuja W, Kumar N, Kumar S, Rizwan A. Precipitating Risk Factors, Clinical Presentation, and Outcome of Diabetic Ketoacidosis in Patients with Type 1 Diabetes. Cureus. 2019;11(5):e4789.
15. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev. 1999;15(6):412-26.
16. Dhatariya K. Blood Ketones: Measurement, Interpretation, Limitations, and Utility in the Management of Diabetic Ketoacidosis. Rev Diabet Stud. 2016;13(4):217-25.
17. Adhikari PM, Mohammed N, Pereira P. Changing profile of diabetic ketosis. J Indian Med Assoc. 1997;95(10):540-2.
18. Slovis CM, Mork VG, Slovis RJ, Bain RP. Diabetic ketoacidosis and infection: leukocyte count and differential as early predictors of serious infection. Am J Emerg Med. 1987;5(1):1-5.
19. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. J Crit Care. 2002;17(1):63-7.
20. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol. 2000;95(11):3123-8.
21. Garg SK, Garg P. Differential Diagnosis of Ketoacidosis in Hyperglycemic Alcoholic Diabetic Patient: Role of Insulin. Indian J Crit Care Med. 2021;25(10):1203-4.
22. Gall AJ, Duncan R, Badshah A. Starvation ketoacidosis on the acute medical take. Clin Med (Lond). 2020;20(3):298-300.
23. Stathi D, Dhatariya KK, Mustafa OG. Management of diabetes-related hyperglycaemic emergencies in advanced chronic kidney disease: Review of the literature and recommendations. Diabet Med. 2025;42(2):e15405.
24. Adeyinka A, Kondamudi NP. Hyperosmolar Hyperglycemic Syndrome. StatPearls. Treasure Island (FL)2025.
25. Dhatariya KK, Nunney I, Higgins K, Sampson MJ, Iceton G. National survey of the management of Diabetic Ketoacidosis (DKA) in the UK in 2014. Diabet Med. 2016;33(2):252-60.
26. Rewers A, Kuppermann N, Stoner MJ, Garro A, Bennett JE, Quayle KS, et al. Effects of Fluid Rehydration Strategy on Correction of Acidosis and Electrolyte Abnormalities in Children With Diabetic Ketoacidosis. Diabetes Care. 2021;44(9):2061-8.
27. Mahler SA, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. Am J Emerg Med. 2011;29(6):670-4.
28. Siwakoti K, Giri S, Kadaria D. Cerebral edema among adults with diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome: Incidence, characteristics, and outcomes. J Diabetes. 2017;9(2):208-9.
29. Pillai S, Davies G, Lawrence M, Whitley J, Stephens J, Williams PR, et al. The effect of diabetic ketoacidosis (DKA) and its treatment on clot microstructure: Are they thrombogenic? Clin Hemorheol Microcirc. 2021;77(2):183-94.
30. Wei WT, Lin SM, Hsu JY, Wu YY, Loh CH, Huang HK, et al. Association between Hyperosmolar Hyperglycemic State and Venous Thromboembolism in Diabetes Patients: A Nationwide Analysis in Taiwan. J Pers Med. 2022;12(2).
31. Burzynski J. DKA and thrombosis. CMAJ. 2005;173(2):132; author reply -3.
32. Li S, Mikhael B, van Zyl DG. Choice of Intravenous Fluid for Resuscitation in Diabetic Ketoacidosis. N Engl J Med. 2025;392(9):923-6.
33. Jahangir A, Jahangir A, Siddiqui FS, Niazi MRK, Yousaf F, Muhammad M, et al. Normal Saline Versus Low Chloride Solutions in Treatment of Diabetic Ketoacidosis: A Systematic Review of Clinical Trials. Cureus. 2022;14(1):e21324.
34. Self WH, Evans CS, Jenkins CA, Brown RM, Casey JD, Collins SP, et al. Clinical Effects of Balanced Crystalloids vs Saline in Adults With Diabetic Ketoacidosis: A Subgroup Analysis of Cluster Randomized Clinical Trials. JAMA Netw Open. 2020;3(11):e2024596.
35. Lizzo JM, Goyal A, Gupta V. Adult Diabetic Ketoacidosis. StatPearls. Treasure Island (FL)2025.
36. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA)2000.
37. Mustafa OG, Haq M, Dashora U, Castro E, Dhatariya KK, Joint British Diabetes Societies for Inpatient Care G. Management of Hyperosmolar Hyperglycaemic State (HHS) in Adults: An updated guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care Group. Diabet Med. 2023;40(3):e15005.
38. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31(11):2081-5.
39. Thammakosol K, Sriphrapradang C. Effectiveness and safety of early insulin glargine administration in combination with continuous intravenous insulin infusion in the management of diabetic ketoacidosis: A randomized controlled trial. Diabetes Obes Metab. 2023;25(3):815-22.
40. Dhatariya KK, Joint British Diabetes Societies for Inpatient C. The management of diabetic ketoacidosis in adults-An updated guideline from the Joint British Diabetes Society for Inpatient Care. Diabet Med. 2022;39(6):e14788.
41. Jiang DH, Herrin J, Van Houten HK, McCoy RG. Evaluation of High-Deductible Health Plans and Acute Glycemic Complications Among Adults With Diabetes. JAMA Netw Open. 2023;6(1):e2250602.
42. Hassan EM, Mushtaq H, Mahmoud EE, Chhibber S, Saleem S, Issa A, et al. Overlap of diabetic ketoacidosis and hyperosmolar hyperglycemic state. World J Clin Cases. 2022;10(32):11702-11.

43. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.
44. Arora S, Cheng D, Wyler B, Menchine M. Prevalence of hypokalemia in ED patients with diabetic ketoacidosis. Am J Emerg Med. 2012;30(3):481-4.
45. Murthy K, Harrington JT, Siegel RD. Profound hypokalemia in diabetic ketoacidosis: a therapeutic challenge. Endocr Pract. 2005;11(5):331-4.
46. Sibai BM, Viteri OA. Diabetic ketoacidosis in pregnancy. Obstet Gynecol. 2014;123(1):167-78.
47. Dhanasekaran M, Mohan S, Erickson D, Shah P, Szymanski L, Adrian V, et al. Diabetic Ketoacidosis in Pregnancy: Clinical Risk Factors, Presentation, and Outcomes. J Clin Endocrinol Metab. 2022;107(11):3137-43.
48. Stathi D, Lee FN, Dhar M, Bobotis S, Arsenaki E, Agrawal T, et al. Diabetic Ketoacidosis in Pregnancy: A Systematic Review of the Reported Cases. Clin Med Insights Endocrinol Diabetes. 2025;18:11795514241312849.
49. Metzger BE, Ravnikar V, Vileisis RA, Freinkel N. "Accelerated starvation" and the skipped breakfast in late normal pregnancy. Lancet. 1982;1(8272):588-92.
50. Nayak S, Lippes HA, Lee RV. Hyperglycemic hyperosmolar syndrome (HHS) during pregnancy. J Obstet Gynaecol. 2005;25(6):599-601.
51. Mohan M BK, Lindow S. Management of diabetic ketoacidosis in pregnancy. . The Obstetrician & Gynaecologist. 2017;19: 55–62.
52. de Veciana M. Diabetes ketoacidosis in pregnancy. Semin Perinatol. 2013;37(4):267-73.
53. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics. 2014;133(4):e938-45.
54. Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013;98(8):3411-9.
55. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? Diabetes Care. 2000;23(10):1556-62.
56. Gavard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes. An epidemiological evaluation. Diabetes Care. 1993;16(8):1167-78.
57. Skinner TC. Recurrent diabetic ketoacidosis: causes, prevention and management. Horm Res. 2002;57 Suppl 1:78-80.
58. Cooper H, Tekiteki A, Khanolkar M, Braatvedt G. Risk factors for recurrent admissions with diabetic ketoacidosis: a case-control observational study. Diabet Med. 2016;33(4):523-8.
59. Mays JA, Jackson KL, Derby TA, Behrens JJ, Goel S, Molitch ME, et al. An Evaluation of Recurrent Diabetic Ketoacidosis, Fragmentation of Care, and Mortality Across Chicago, Illinois. Diabetes Care. 2016;39(10):1671-6.
60. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med. 2006;144(5):350-7.
61. Lebovitz HE, Banerji MA. Ketosis-Prone Diabetes (Flatbush Diabetes): an Emerging Worldwide Clinically Important Entity. Curr Diab Rep. 2018;18(11):120.
62. Mauvais-Jarvis F, Sobngwi E, Porcher R, Riveline JP, Kevorkian JP, Vaisse C, et al. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes. 2004;53(3):645-53.
63. Banerji MA, Chaiken RL, Lebovitz HE. Long-term normoglycemic remission in black newly diagnosed NIDDM subjects. Diabetes. 1996;45(3):337-41.
64. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab. 2003;88(11):5090-8.
65. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The Global Epidemiology of Diabetes and Kidney Disease. Adv Chronic Kidney Dis. 2018;25(2):121-32.
66. Kim HJ. Metabolic Acidosis in Chronic Kidney Disease: Pathogenesis, Clinical Consequences, and Treatment. Electrolyte Blood Press. 2021;19(2):29-37.
67. Al Sadhan A, ElHassan E, Altheaby A, Al Saleh Y, Farooqui M. Diabetic Ketoacidosis in Patients with End-stage Kidney Disease: A Review. Oman Med J. 2021;36(2):e241.
68. Galindo RJ, Pasquel FJ, Vellanki P, Zambrano C, Albury B, Perez-Guzman C, et al. Biochemical Parameters of Diabetes Ketoacidosis in Patients with End-stage Kidney Disease and Preserved Renal Function. J Clin Endocrinol Metab. 2021;106(7):e2673-e9.
69. Sudha MJ, Salam HS, Viveka S, Udupa AL. Assessment of changes in insulin requirement in patients of type 2 diabetes mellitus on maintenance hemodialysis. J Nat Sci Biol Med. 2017;8(1):64-8.
70. Galindo RJ, Pasquel FJ, Fayfman M, Tsegka K, Dhruv N, Cardona S, et al. Clinical characteristics and outcomes of patients with end-stage renal disease hospitalized with diabetes ketoacidosis. BMJ Open Diabetes Res Care. 2020;8(1).
71. Seddik AA, Bashier A, Alhadari AK, AlAlawi F, Alnour HH, Bin Hussain AA, et al. Challenges in management of diabetic ketoacidosis in hemodialysis patients, case presentation and review of literature. Diabetes Metab Syndr. 2019;13(4):2481-7.
72. Gupta A, Rohrscheib M, Tzamaloukas AH. Extreme hyperglycemia with ketoacidosis and hyperkalemia in a patient on chronic hemodialysis. Hemodial Int. 2008;12 Suppl 2:S43-7.

73. Ting S, Chua HR, Cove ME. Euglycemic Ketosis During Continuous Kidney Replacement Therapy With Glucose-Free Solution: A Report of 8 Cases. Am J Kidney Dis. 2021;78(2):305-8.
74. Coutrot M, Hekimian G, Moulin T, Brechot N, Schmidt M, Besset S, et al. Euglycemic ketoacidosis, a common and underecognized complication of continuous renal replacement therapy using glucose-free solutions. Intensive Care Med. 2018;44(7):1185-6.
75. Rajdev K, Leifer L, Sandhu G, Mann B, Pervaiz S, Habib S, et al. Fluid resuscitation in patients with end-stage renal disease on hemodialysis presenting with severe sepsis or septic shock: A case control study. J Crit Care. 2020;55:157-62.
76. Kanbay M, Copur S, Mizrak B, Ortiz A, Soler MJ. Intravenous fluid therapy in accordance with kidney injury risk: when to prescribe what volume of which solution. Clin Kidney J. 2023;16(4):684-92.
77. Hurtado CR, Lemor A, Vallejo F, Lopez K, Garcia R, Mathew J, et al. Causes and Predictors for 30-Day Re-Admissions in Adult Patients with Diabetic Ketoacidosis in the United States: A Nationwide Analysis, 2010-2014. Endocr Pract. 2019;25(3):242-53.
78. Culica D, Walton JW, Prezio EA. CoDE: Community Diabetes Education for uninsured Mexican Americans. Proc (Bayl Univ Med Cent). 2007;20(2):111-7.
79. Prezio EA, Pagan JA, Shuval K, Culica D. The Community Diabetes Education (CoDE) program: cost-effectiveness and health outcomes. Am J Prev Med. 2014;47(6):771-9.
80. Lam D, Shaikh A. Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics. Kidney360. 2021;2(4):742-6.