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DIABETES AND METABOLIC DISEASE (W FORD, SECTION EDITOR)

Diabetic Ketoacidosis: A Review and Update

Gretchen Perilli · Christine Saraceni · Michael N. Daniels · Aakif Ahmad

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Abstract Diabetic ketoacidosis (DKA) remains a significant complication of diabetes in both the United States and around the world. Diabetic ketoacidosis remains a significant complication of diabetes in both the United States and worldwide with its associated high rates of hospital admissions. Therefore, it becomes vital that the healthcare professional be able to manage the hyperglycemic crises associated with diabetes. Moreover, with increasing healthcare costs and a changing healthcare system, prevention of diabetic ketoacidosis remains essential. Though management of diabetic ketoacidosis has followed a set algorithm for many years, there are exciting management alternatives on the horizon such as subcutaneous insulin administration for uncomplicated DKA patients. By understanding DKA, including its pathogenesis, presentation, treatment, and prevention, admissions may be decreased and length of stay shortened.

G. Perilli (✉)
Division of Endocrinology, Department of Internal Medicine, Lehigh Valley Hospital and Health Network, 1243 South Cedar Crest Blvd, Suite 410, Allentown, PA 18103, USA
e-mail: Gretchen_A.Perilli@LVH.COM

C. Saraceni · M. N. Daniels · A. Ahmad
Department of Internal Medicine, Lehigh Valley Hospital and Health Network, 1255 South Cedar Crest Blvd, Suite 410, Allentown, PA 18105, USA
e-mail: Christine.Saraceni@lvhn.org

M. N. Daniels
e-mail: Michael_N.Daniels@lvhn.org

A. Ahmad
e-mail: Aakif.Ahmad@lvhn.org

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Introduction

There are two major hyperglycemic crises associated with diabetes: diabetic ketoacidosis and the hyperosmotic hyperglycemic state. There are ~120,000 admissions for diabetic ketoacidosis and hyperglycemic hyperosmolar state per year in the United States alone [1]. Diabetic ketoacidosis primarily results from insulin deficiency and hyperglycemic hyperosmolar state (HHS) from severe insulin resistance. Both of the crises result in subsequent glucagon and counter-regulatory hormone excess from lack of suppression from insulin [2•]. Normally, with elevated blood glucose, as occurs after a digested meal, there is production and release of insulin by the beta cells in the islets of Langerhans. With this surge of insulin, the production of new glucose is suppressed appropriately. Conversely, in a state of starvation, there is an increase in counter regulatory hormones such as glucagon in which stores are appropriately mobilized and glucose production increased. This is a catabolic state, which allows for sustenance in times when nutrition is not available [3, 4].

Pathogenesis

In diabetic ketoacidosis (DKA), the balance between catabolism and anabolism is, in a sense, broken. With the lack of insulin, there is decreased storage of glucose, increased breakdown of glycogen stores, and increased synthesis of glucose in both the liver and kidney. To add to

the overall hyperglycemic state, there is also a concomitant decreased utilization of glucose in peripheral tissues [2•, 3]. The situation is complicated by the fact that in this more catabolic state there is breakdown of proteins to form new amino acids that in turn are used to build glucose [2•, 3]. Moreover, the risk of DKA increases with any increased stress state. In a so-called "stressed state," there is a relative abundance of epinephrine and cortisol. Epinephrine acts to block the action of insulin and stimulates the release of glucagon. Growth hormone also has a similar role as epinephrine and cortisol. In a stressed state, such as infection, myocardial infarction, intoxication, pregnancy, or stroke there is an increased demand for insulin, but a diminished supply by the stress put on the pancreas [1, 5].

While elevated blood glucose from the increased glycogenolysis and gluconeogenesis is certainly a major problem, the cornerstone of DKA lies in ketogenesis. Insulin is normally the most important regulator in production and utilization of ketones. Insulin will inhibit lipolysis and oxidation of free fatty acids. Insulin also increases oxidation of ketones in the peripheral tissues [6]. Thus there is both overproduction and underutilization of ketones in an insulin-deficient state [6]. Also, glucagon itself will stimulate hormone-sensitive lipase, which in turn mobilizes adipose stores and converts triglycerides to free fatty acids [2•]. These free fatty acids are then transported across the mitochondrial membrane, and they are eventually used for synthesis of ketones, namely in the form of acetoacetic acid, which is oxidized to form beta-hydroxybutyrate or decarboxylated to form acetone. Unfortunately, with ketone overproduction, peripheral tissues cannot utilize these molecules and ketosis predominates [7]. Conversely, in HHS there is usually enough insulin to suppress ketogenesis, but not control blood sugars [8]. In HHNK, blood sugars are usually higher as ketoacidosis produces more severe symptoms and presentation is usually earlier.

Symptoms of ketosis include nausea, vomiting, abdominal pain, and respiratory insufficiency. Increased ketone production results in the attempt for the body to buffer with bicarbonate. Because of this buffering, there is an increase in unmeasured anions that cause a gapped metabolic acidosis. Vomiting may induce a hidden alkalosis. Furthermore, with the pre-renal azotemia that ensues, there is retention of other acids besides ketoacids [6].

Many of the remaining problems with DKA are from the resultant osmotic diuresis. Elevated blood glucose shifts water into the extracellular compartment. However, the expansion of the extra-cellular compartment is short lived as the ability to reabsorb glucose at the level of the renal tubule is limited and osmotic diuresis occurs. Thus, glycosuria and polyuria result. Water losses are typically greater than electrolyte losses, and thus there is an increased serum osmolality [6]. Polydipsia results from the hyperosmolarity after osmoreceptors are triggered in the brain. Many of the other symptoms may result from the pro-inflammatory state of DKA, and elevated cytokines have been documented during diabetic ketoacidosis [9]. Sodium tends to be low secondary to the fact that glucose is osmotically active and will draw fluids into the extracellular space. Potassium is variable based on the degree of acidosis and the time of presentation of the DKA.

Management of Adult Patients with Diabetic Ketoacidosis

Initial Evaluation

DKA usually occurs quickly, over hours to days. Patients may have symptoms of hyperglycemia, including polyuria, polydipsia, polyphagia, and weight loss. The more acute symptoms include abdominal pain, vomiting, dehydration, weakness, altered mentation, and coma. Abdominal pain must be worked up carefully, as an abdominal process may have precipitated the ketoacidosis state. Findings on examination include increased skin turgor, Kussmaul respirations, tachycardia, hypotension, altered mentation, and coma [10]. Hypothermia may also be present. In a hypothermic patient normal body temperatures may signal an infection [11].

Though the majority of patients presenting with DKA are type 1 diabetics, ketosis-prone type 2 diabetics have been described. These patients may represent 20 % of DKA patients. They are typically middle-aged obese persons of varying ethnic backgrounds. After the acute hospitalization, these patients are usually able to discontinue insulin therapy for months to years, and may be treated with oral diabetic medications [12]. The most common metabolic abnormalities in DKA are summarized in Table 1.

Identification of co-morbid inciting events including infection, cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, new onset diabetes, hyperthyroid state, medications, and insulin noncompliance is paramount to successful management [13, 14, 15•]. Initial laboratory evaluation should include serum glucose, electrolytes with calculated anion gap, plasma osmolality, BUN, creatinine, urinalysis (serum ketones if urine ketones positive), CBC with differential,

Table 1 Common laboratory findings in diabetic ketoacidosis (DKA)

Plasma glucose (mg/dL)	200–600
Osmolality (mOsm/L)	300–320
Ketones	Present
Blood pH	<7.30
Serum anion gap (mEq/L)	>16
Serum bicarbonate (mmol/L)	<15

ABG if serum bicarbonate is substantially reduced, and EKG. Supplemental testing including chest X-ray, cultures, and HgA1C is performed as indicated [13]. Successful management and therapeutic goals include strict monitoring of clinical and laboratory parameters with correction of hyperglycemia, electrolyte imbalances, improving circulatory volume and tissue perfusion; identifying and treating precipitating events irrespective of the type of diabetes is also paramount to successful care [16–18]. The optimal care site (intensive care unit, step-down unit or medical ward) has not been substantiated in randomized prospective studies for the treatment of DKA. Consequently, patients are triaged based on known prognostic indicators, clinical status, availability of resources and institutional policy [18]. The development of written therapeutic guidelines and interdisciplinary collaboration has standardized care and led to better outcomes [19, 20] (Fig. 1). With a systematic approach to treatment clinical stability is typically achieved within 12–36 h [1].

Other causes of an anion gap acidosis should be kept in mind when reviewing blood work, particularly if ketones are not elevated in a hyperglycemic patient. Lactic acidosis may be present either alone or with diabetic ketoacidosis and signals poor tissue oxygenation. Starvation ketosis results from poor carbohydrate availability. In starvation ketosis, the anion gap will be mildly elevated. Ketones may be present in the urine but rarely in the blood. In long-standing alcoholics, alcoholic ketoacidosis should be considered. Acidosis may also occur from ingested toxins including salicylates, methanol, and ethylene glycol [10].

Monitoring

Blood monitoring should occur every 2–4 h, including serum electrolytes, renal function, CO2 content and pH [1, 13, 18]. Venous pH monitoring demonstrates a 0.03 unit level of agreement with arterial values and may be an acceptable surrogate for arterial measurements and may

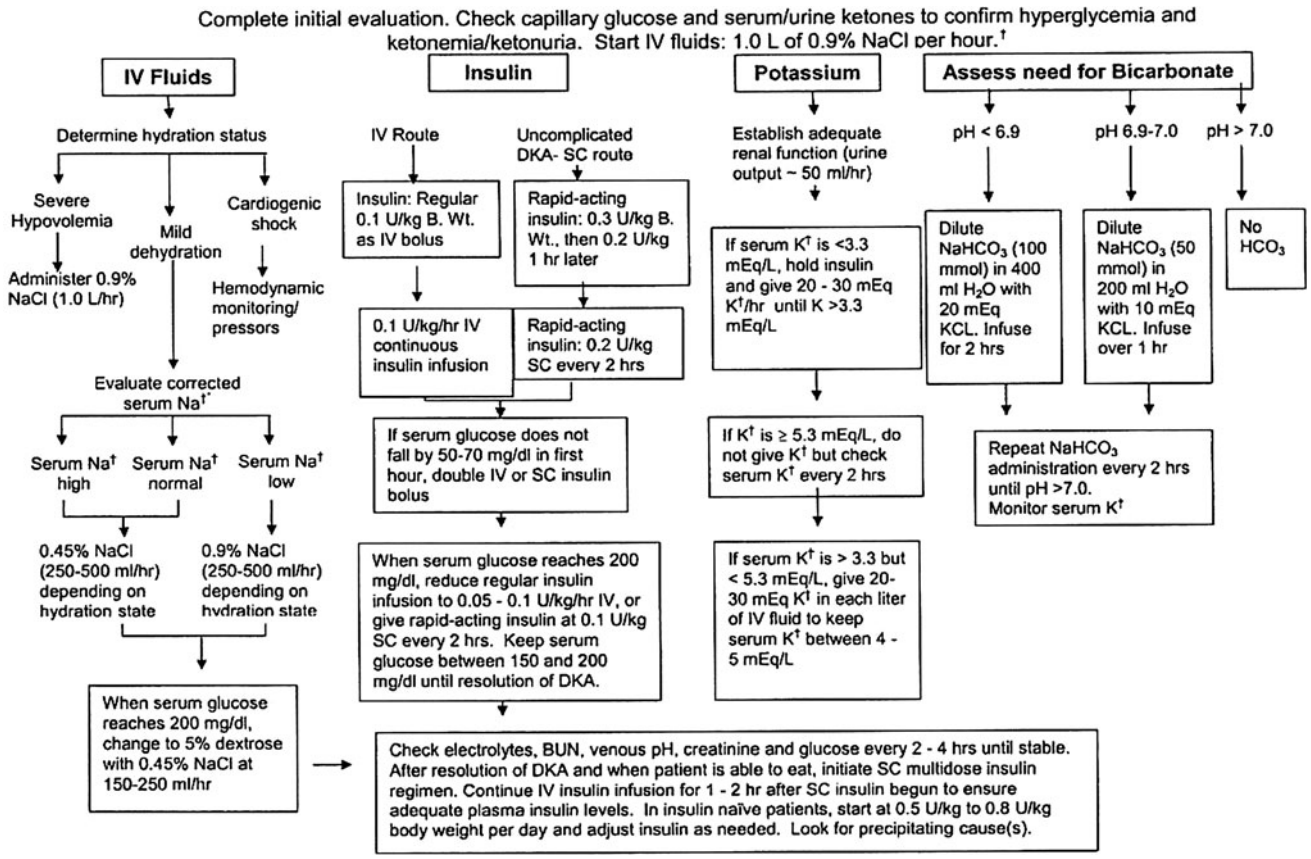

Fig. 1 Protocol for the management of adult patients with DKA. Copyright 2006 American Diabetes Association, From Kitabchi et al. [20], Reprinted by permission of *The American Diabetes Association*. *DKA diagnostic criteria: serum glucose >250 mg/dl, arterial pH <7.3, serum bicarbonate <18 mEq/l, and moderate ketonuria or ketonemia. Normal laborarory values vary; check local lab normal ranges for all electrolytes. †After history and physical exam, obtain capillary glucose and serum or urine ketones (nitroprusside method). Begin 1 liter of 0.9 % NaCl over 1 h and draw arterial blood gases, complete blood count with differential, urinalysis, serum glucose, blood urea nitrogen (BUN), electrolytes, chemistry profile, and creatinine levels STAT. Obtain electrocardiogram, chest X-ray, and specimens for bacterial cultures, as needed. ‡Serum Na^+ should be corrected for hyperglycemia (for each 100 mg/dl glucose >100 mg/dl, add 1.6 mEq to sodium value for corrected serum sodium value). Adapted from Reference [1]

reduce the intensity of arterial sampling [21]. Serum glucose should be monitored more closely on an hourly basis until blood glucose reaches 250 mg/dL and the clinical condition stabilizes wherefrom glucose levels may be checked every 1–2 h [18, 22]. The serum bicarbonate trend and anion gap are valuable indices of therapeutic response [1, 13]. Ketonemia may persist despite clearing of hyperglycemia [16] therefore closure of the anion gap is a better monitoring parameter [13].

Volume Status/Fluid Replacement

Aggressive rehydration and amelioration of the hyperosmolar state may enhance the effect of low-dose insulin therapy. Initial fluid resuscitation goals include expansion of the intravascular, interstitial and intracellular volume and restoration of renal perfusion [13, 15•, 18, 23, 24]. To adequately assess the severity of sodium and water deficit, the serum sodium is corrected by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose above 100 mg/dL [15•, 18]. The use of normal saline (0.9 %) pervades the existing guidelines for initial resuscitation [15•, 16]. This is accomplished over the first hour with isotonic saline (0.9 % sodium chloride) with an infusion rate of 15–20 mL/Kg lean body weight per hour unless contraindicated due to cardiovascular or renal compromise and the risk of iatrogenic volume overload (average adult ~1–1.5 L/h) [15•, 18]. Patients in shock may require a more rapid rate of infusion. Initial volume re-expansion should not exceed 50 mL/kg in the first 4 h. Thereafter fluid replacement is guided by clinical exam, hemodynamics, hydration status, serum electrolyte levels, and urine output [15•, 25]. The severity of dehydration and volume depletion can be estimated using the following guidelines in close comparison with the clinical examination: (1) steady state blood pressure with an increase in orthostatic pulse indicates a 10 % decrease in extra cellular volume (~2 L deficit), (2) an orthostatic drop in blood pressure (>15/10 mmHg) indicates a 15–20 % decrease in extra cellular volume (~3–4 L deficit) and (3) supine hypotension indicates a decrease of >20 % in extra cellular fluid volume (>4 L deficit) as defined by Kitabchi et al. [18]. A complication of large volume intravenous saline resuscitation during the initial treatment of DKA is the development of hyperchloremic non-anion gap metabolic acidosis, which is usually transient [18, 26] and resolves within 24–48 h with enhanced renal excretion [18]. A recent randomized controlled trial failed to demonstrate superiority with Ringer's lactate when used in the acute treatment of DKA [27].

Ultimately the total volume deficit should be replete within the first 24 h, with half of the estimated total body deficit given over the first 8–12 h [22]. In patients with normal or elevated corrected serum sodium, 0.45 % sodium chloride is the replacement fluid of choice infused at a rate of 4–14 mL/kg per hour [in the range of 250–500 ml/h]. Isotonic saline at a comparable rate may be continued if the corrected serum sodium is low [15•, 16, 25]. Dextrose should be added to intravenous fluids when blood glucose falls to <200–250 mg/dL [1, 18].

Potassium Replacement

Severe insulin deficiency, hyperosmolality, and acidemia may cause spuriously elevated levels of serum potassium despite total-body potassium deficiency [13, 15•]. During the acute treatment of DKA, serum potassium concentration may precipitously decline as potassium is driven into the intracellular compartment [18]. Initially the serum potassium should be checked every 1–2 h over the first 5 h of treatment as the most dramatic changes occur during this period [16]. Potassium replacement is initiated when the serum potassium concentration falls below the upper level of normal for a given laboratory (typically <5.3 mEq/L) in the setting of adequate renal perfusion and urine output with a goal range of serum potassium between 4.0 and 5.0 mEq/L [15•, 28]. As a rule, potassium chloride (20–30 mEq/L) is added to each liter of one-half isotonic saline to accomplish this goal [13, 15•]; however, additional doses may be necessary [27]. One-third of potassium replacement may be administered as potassium phosphate to offset the chloride load given with intravenous fluids and to prevent hypophosphatemia [18]. Rarely, severe total-body potassium depletion manifests as low or low-normal serum potassium levels on admission and requires aggressive repletion to avert cardiac dysrhythmia or cardiopulmonary distress, as vigorous treatment potentiates further decline [13, 15•]. Initiation of insulin therapy is withheld until potassium deficits are corrected when serum potassium is <3.3 mEq/L. If serum potassium is >5.3, potassium chloride supplementation is held and serum potassium levels are monitored closely every 2 h [14].

Insulin Therapy: Intravenous Insulin and Subcutaneous Transition

Insulin therapy may exacerbate hypokalemia and its consequences; therefore, initiation of insulin should be delayed until serum potassium reaches 3.3 mEq/L and should ensue after intravascular volume expansion. Traditionally, a continuous intravenous infusion of regular insulin is the treatment of choice to inhibit lipolysis with the exception of mild episodes of DKA [13, 14, 29, 30]. The mainstay of DKA treatment with intravenous regular insulin occurs in the intensive care setting due to technical constraints, concomitant life-threatening illnesses and institutional

policy [15•, 31]. The standard is an initial intravenous bolus of regular insulin 0.1 units/kg body weight followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h [1, 13, 18, 28, 31]. Alternatively, an intravenous infusion alone of regular insulin at a starting rate of 0.14 units/kg/h (~10 units/h in a 70-kg patient) without the priming loading dose has recently been proposed in a prospective randomized study [25]. The acute intravenous treatment of DKA can also be initiated with insulin glulisine, however selection is guided by institutional preference and cost-containment [30]. The expected fall in serum glucose concentration within the first hour is 50 mg/dL. If this is not attained, re-address hydration status then titrate insulin infusion by doubling every hour until a steady glucose decline between 50 and 75 mg/h is achieved [13, 15•, 18]. When the serum glucose reaches ~200–250 mg/dL the insulin infusion rate is decreased to 0.02–0.05 units/kg per hour and dextrose (5–10 %) is added to the intravenous fluids to prevent precipitous falls in plasma osmolality, thereby allowing continued insulin administration with the goal serum glucose between 140 and 200 mg/dL and resolution of metabolic acidosis [1, 13, 14, 15•, 18].

The ideal route of insulin administration remains debatable in the acute treatment of DKA and includes regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections [14, 15•, 25, 29, 31–33]. Overwhelmingly, experts have recommended intravenous insulin infusion as the treatment of choice in the intensive care setting, as it is a predictable means of administration allowing for maximal peak insulin within the first hour of treatment [15•, 25, 29]. In mild, uncomplicated cases of DKA a subcutaneous regimen of newer rapid-acting insulin analogues (insulin aspart, lispro, glulisine) have been proposed as safe and effective alternatives to the use of intravenous regular insulin in prospective, randomized trials [14, 30, 31]. Subcutaneous analogs may be more cost-effective on the general wards compared to treatment with intravenous regular insulin in the intensive care unit in patients without major co-morbidities [31]. Barriers include inadequacy of nursing staff on general ward floors to implement the strict monitoring protocol. Regimens include subcutaneous rapid-acting insulin aspart or lispro loading dose of 0.3 units/kg body weight followed by subcutaneous insulin aspart or lispro at 0.1 units/kg/h until blood glucose levels <200–250 mg/dL. At this juncture, intravenous fluids are switched to a dextrose-containing solution and the rapid-acting analog dose is reduced (0.05–0.1 units/kg/h) to maintain serum glucose of 200 mg/dL until resolution of diabetic ketoacidosis [14, 31, 32]. This approach is utilized less frequently in the clinical setting, possibly due to titration difficulties with longer half-life preparations or familiarity with standard insulin infusions [1].

The following criteria mark the resolution of DKA according to the ADA guidelines: glucose <200 mg/dL, serum bicarbonate ≥18 mEq/L, serum anion gap <12 mEq/L and a venous pH of >7.3 [14]. Once the acidosis has resolved with normalization of the anion gap and the patient is tolerating PO intake, a subcutaneous insulin regimen can be initiated which includes a combination of short- or rapid-acting and intermediate- or long-acting insulin as needed to maintain blood glucose control [13] in the range of 90–140 mg/dL. More recently, a regimen of long-acting basal insulin (i.e., glargine) and rapid-acting insulin analogs (i.e., lispro, aspart, glulisine) has been recommended as a more physiological approach for glucose control in in patients with a low incidence of hypoglycemic events [30, 34]. Upon this transition, a 1–2 h overlap with the intravenous insulin infusion must occur to prevent a precipitous decrease in serum insulin levels and the re-development of hyperglycemia and ketoacidosis [13, 15•, 18, 30]. In patients who are NPO at the close of the anion gap, the intravenous insulin infusion should be maintained and supplemented with subcutaneous regular insulin as needed every 4 h in 5-unit increments for every 50 mg/dL increase in blood glucose above 150 mg/dL [13, 18]. In a prior diabetic on a home insulin regimen, their home dose of insulin may be resumed with adjustments made for target serum glucose control. In the insulin-naïve patient, the initial basal dose of long-acting insulin should be 0.5–0.8 units/kg per day with a fractionated schedule of short-acting bolus insulin with adjustments to maintain target serum glucose [13, 18, 30]. If appropriate, oral antihyperglycemic therapy and nutrition counseling can be implemented at discharge for some type 2 diabetics [13].

Bicarbonate Therapy

Bicarbonate replacement is a controversial issue and a unified consensus is lacking. Currently, there are no prospective randomized trials to evaluate the utility of bicarbonate therapy in DKA with severe metabolic acidosis (pH <6.9), and to date the use of bicarbonate has been unsubstantiated in small clinical trials. Alkali therapy in DKA has not been routinely recommended, as metabolic derangements tend to correct with insulin therapy and fluids as hypovolemia, tissue perfusion and renal function improve [18, 22]. In a small randomized prospective study, the administration of bicarbonate in severe diabetic ketoacidosis (arterial pH 6.9–7.14) did not significantly affect the rate of glucose decline, ketone levels or correction of acidosis [32, 35]. Other studies found no significant difference with bicarbonate infusion compared to saline in altering blood glucose concentration and, conversely, bicarbonate may impair ketone and lactate clearance [36]. Paucity of data on beneficial versus adverse effects of

bicarbonate therapy have limited its recommended use to severe acidosis [37, 38] and electrocardiographic hyperkalemic changes [1]. Proponents of alkali therapy argue severe metabolic acidosis is associated with intracellular acidosis and end organ dysfunction, particularly its deleterious cardiopulmonary effects [18, 39, 40]. As a consequence of the increased severity of metabolic acidosis with pH <7.0, bicarbonate may empirically be given as an isotonic solution with an initial dose of 50 mmol intravenous bicarbonate (one ampoule of 7.5 % $NaHCO_3$ solution in 250 ml sterile water) with 15 mEq of KCL for each ampoule of bicarbonate administered if serum potassium <5.5 mEq/L [18]. Alternatively, if the pH is <6.9, 100 mmol (100 mEq) administered in 400 mL sterile water may be infused at 200 mL/h with frequent re-dosing every 2 h until pH exceeds 7.0 [1, 15•, 22]. Further research is needed for its use as an adjunctive therapy.

Phosphate Therapy

Whole-body phosphate depletion is a hallmark of poorly controlled diabetes and typically remains asymptomatic [13]. Hyperglycemia and hyperosmolarity cause an intracellular to extracellular shift of serum phosphate. For this reason, serum phosphate levels may be normal or increased at the onset of DKA [15•, 18]. Insulin therapy in the setting of DKA may unveil hypophosphatemia as insulin drives phosphate back into cells. This is typically inconsequential until serum phosphate levels fall to <1.0 mg/dL or, in patients with cardiac dysfunction, skeletal muscle weakness, respiratory failure or hemolytic anemia arise [13, 18, 32, 41]. In these instances, potassium or sodium phosphate supplementation (20–30 mEq/L) may be added to replacement fluids over several hours [1, 18] with close monitoring of serum calcium and phosphate levels [18, 41]. Alternatively, in patient tolerating oral intake with mild deficits, oral phosphate (2.5–3.5 g/day in 2–3 divided doses may be administered [1]. Prospective randomized trials have failed to demonstrate a measurable clinical benefit with phosphate therapy in amelioration of the duration of DKA, insulin requirements, hyperglycemia or effect on morbidity and mortality [32, 41].

Complications

The most widely recognized complications of DKA treatment include exogenous insulin-induced hypoglycemia and hypokalemia. The effect of bicarbonate therapy may also worsen hypokalemia. These complications may be avoided with the use of dextrose-containing solutions when blood glucose falls below 250 mg/dL with a concomitant reduction in the rate of insulin delivery as well as the addition of potassium to replacement fluids [18, 28]. Additionally, abrupt discontinuation of intravenous insulin therapy after resolution of DKA without overlapping subcutaneous insulin coverage may precipitate hyperglycemia [13].

Although rare in adult patients, cerebral edema is a complication of DKA treatment with significant morbidity and mortality [16, 18, 23]. Its hallmarks include rapid deterioration in the level of consciousness and headache. Other manifestations include seizure, bradycardia, incontinence, respiratory arrest, and eventual brain-stem herniation. Theoretically, cerebral edema develops when water is osmotically driven into the central nervous system; plasma osmolality declines too rapidly during replacement of sodium and water deficits in DKA treatment [13]. Gradual correction of the hyperosmolar state in addition to adding dextrose to intravenous fluids when blood glucose falls below 250 mg/dL may avert this risk.

Hypoxemia and noncardiogenic pulmonary edema may result secondary to falling colloid osmotic pressure and subsequent increase in lung water content and diminished lung compliance [13]. A rare but highly morbid complication of DKA is ARDS [42]. Ominous signs include a widened A-a gradient, dyspnea, hypoxemia, rales or infiltrates during routine resuscitation as well as severe acidemia [42]. Lastly, vascular thrombosis may occur in the setting of critical illness and low dose heparin or low molecular weight heparin should be considered for prophylaxis [16].

Prevention

Once a patient is successfully treated and transitioned to a subcutaneous insulin regimen the focus should turn to prevention of future episodes. Efforts should be made to ensure the patient has a grasp of their condition, close physician follow-up, and access to their medications. Patient education should occur as soon as the patient is well enough to participate. Inpatient education should include an assessment of the patients understanding of diabetes, information regarding physiology of diabetes, and overall treatment goals. The medical team should review sick-day plans with patients. The patient should be more vigilant on days with fevers, vomiting, or diarrhea. Sick-day plans should include more frequent monitoring of blood sugars, every 4–6 h, and checking for ketones. This should allow the patient to detect ketosis early and allow delivery of increased doses of insulin as planned by their specialist to prevent severe hyperglycemia. The patient should also be encouraged to continue nutrition and fluid intake and to seek medical attention if they are unable to tolerate oral intake. If symptoms of DKA are present or hyperglycemia with sustained capillary blood sugars greater than 240 mg/dL medical attention should be sought [43]. Patients should

be discharged on cost-effective regimens with close follow up with their primary care providers.

Conclusion

With the combination of interdisciplinary collaboration and standardized care the mortality of DKA has decreased significantly in the past few decades [32]. The challenges for current practitioners include triaging DKA patients to the appropriate level of care and educating patients to avert repeat episodes of DKA. The potential cost saving associated with caring for less severe DKA patients in medical floors must be weighed with staffing ratios. The prevention of DKA will require further study and collaboration between inpatient and outpatient practitioners, as well as patient education.

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