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Diabetic ketoacidosis

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ABSTRACT

Diabetic ketoacidosis (DKA) is a form of a hyperglycemic emergency mainly characterized by the triad of hyperglycemia, ketosis, and anion gap metabolic acidosis. DKA may be the initial presentation in approximately 25-40 % of patients with type 1 diabetes. It may also occur in at least 34% of patients with type 2 diabetes. DKA has economic as well as medical implications. This review aims to explore and discuss diabetic ketoacidosis, its pathophysiology, clinical presentation, diagnosis, and management, including nuances in special populations such as pediatrics, obstetrics, and patients with chronic kidney disease.

Introduction

Diabetic ketoacidosis (DKA) is a form of a hyperglycemic emergency mainly characterized by the triad of hyperglycemia, ketosis, and anion gap metabolic acidosis. DKA most commonly occurs in type 1 diabetes but may occur in patients with type 2 diabetes. Euglycemic DKA (eDKA), an atypical presentation of DKA with normal to moderate hyperglycemia, is another variant of DKA and hyperglycemic emergencies. Despite the discovery and development of diagnostic tests, medications, and technology, DKA remains one of the leading causes of morbidity and mortality in patients with diabetes.[1–7]

Brief historical perspective

DKA was first described in 1886 by Dr. Julius Dreschfeld during a lecture to the Royal College of Physicians on the topic of Diabetic coma. He expounded on symptoms and physical exam findings, and described the presence of glucose, albumin, aceto-acetic acid, and beta-oxy butyric acid in the urine as well as the characteristic acetone in both urine and breath of the patients. He also attempted to briefly discuss several treatment modalities available during his time, including Intravenous administration of phosphate of soda and chloride of sodium and bicarbonate of soda, all proved to be ineffective at best

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in preventing patient deaths.[5,8] It was not until 1922, a year after insulin was successfully extracted and isolated by Dr. Banting and Best, that insulin was used in a 14-year-old patient with severe juvenile diabetes with ketosis and showed marked improvement and recovery.[5,9] Most of our understanding of DKA pathophysiology and treatment was described in the 1970s. Roger Unger (in 1971) described DKA as a disorder of insulin and glucagon ratio.[10,11] Kitabachi et al in the 1970s showed that small doses of intravenous insulin are effective in treating DKA.[12] In 1973, Munro et al. described a new entity of diabetic metabolic ketoacidosis without severe hyperglycemia where blood glucose is less than 300 mg/100 ml and called it "euglycemic diabetic ketoacidosis".[13,14] Such eDKA variant gained more importance in 2015 when the FDA issued a drug safety communication regarding sodium-glucose cotransporter-2 (SGLT-2) inhibitors causing ketoacidosis.[15]

Epidemiology

DKA may be the initial presentation in approximately 25-40 % of patients with type 1 diabetes. It may also occur in at least 34% of patients with type 2 diabetes. DKA has economic as well as medical implications. In 2010 the Centers for Disease Control and Prevention (CDC) reported that patients with type 2 diabetes accounted for 33,000 out of 142,000 DKA hospitalizations. They also reported in 2016 around 188,000 admissions with DKA among US adults, which is about 9.1 per 1,000 adults with diabetes.[16,17]

Younger patients (18-44 years old) has a higher rate of admissions and lower mortality while older patients with more comorbidities have lower hospitalization trends but higher mortality.[18] DKA hospitalizations have shown a declining trend at a rate of 1.1% from 2000 to 2009 when adjusted for age.[19] However, between the years 2009 to 2014, the trend reversed and showed an age-adjusted rate increase at a rate of 6.3%. A study on DKA incidence in type 1 diabetes in US commercially insured patients reported a similar trend and an overall incidence of 55.5 per 1000 person-years.[20] In patients older than 18 years of age, such incidence is around 44.8 per 1000 person-years and about 108 per 1000 person-years in the pediatric population[18,19,20]

The ADA reports a DKA risk of around 1-10 per 100 person-years in children and adolescents with type 1 diabetes.[21] From 2002 to 2010, the SEARCH for Diabetes in Youth Study- a multisite population-based US study of youth onset diabetes- reported that around 30% of young (youth) patients with type 1 diabetes present with DKA. This was much less common in youths with type 2 diabetes.[22] A follow-up study from 2010 to 2016, showed an increase in prevalence for people with type 1 diabetes to approximately 40%.[23] This correlates with the study done by Praveen et al., which showed the prevalence of DKA in the pediatric population had a significant upward trend after 2010.[21,24] DKA mortality rates have been on a steady declining trend with case-fatality rates as low as 0.4% in 2014[19] and 0.38% in 2017.[25]

Pathophysiology

The primary pathophysiologic mechanism of DKA is caused by an imbalance in the ratio of insulin and counterregulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone. The absolute or relative insulin insufficiency results in increased hepatic gluconeogenesis and glycogenolysis. An increase in catecholamines and cortisol levels leads to protein catabolism, causing increased gluconeogenic amino acid precursors such as alanine, lactate, and glycerol. Glucagon stimulates glycogenolysis. There is also a loss of insulin-dependent glucose transport and utilization in peripheral tissues resulting in hyperglycemia.[1,2,5]

The hormonal imbalance with decreased insulin and the relative increase of catecholamines, cortisol, and growth hormone activates the hormone-sensitive lipase resulting in the breakdown of triglycerides, therefore, releasing free fatty acids. This also leads to a decreased level of malonyl coenzyme A; with a reciprocal stimulation of carnitine palmitoyl acyltransferase (CPTI) that transports fatty acids into the hepatic mitochondria. Once in the hepatic mitochondria, the free fatty acids undergo beta-oxidation to generate acetyl-coenzyme A and, in turn, cause increased keto acid production. The two ketone bodies that accumulate are acetoacetic acid and beta-hydroxybutyrate, resulting in ketonemia. Both acetoacetic acid and beta-hydroxybutyrate are strong acids. They produce a large number of hydrogen ions when they dissociate. Typically, hydrogen ions are buffered by bicarbonate; however, because there is an overproduction of hydrogen ions, the buffering capacity is overwhelmed and leads to anion gap metabolic acidosis.[1,2,5] See Fig. 1.

Hyperglycemia above the renal threshold 10.1-11.2 mmol/L (>180-200 mg/dL) results in glycosuria. This produces an osmotic diuresis that drags solutes such as sodium, potassium, chloride, and phosphorus along with it, leading to dehydration and electrolyte losses. There may be poor perfusion of peripheral tissues with significant dehydration, leading to lactic acidosis, which further aggravates the existing ketoacidosis.[1,2,5]

The pathophysiologic mechanism of eDKA is also caused by an imbalance in the ratio of insulin and the counterregulatory hormones with a state of carbohydrate deficit.[1]

Precipitating factors

In the pediatric population, DKA is most commonly the initial presentation of type 1 diabetes. In patients known to have diabetes, DKA may be precipitated by an infection, poor medication compliance, or technology failure such as pump malfunction.[26]

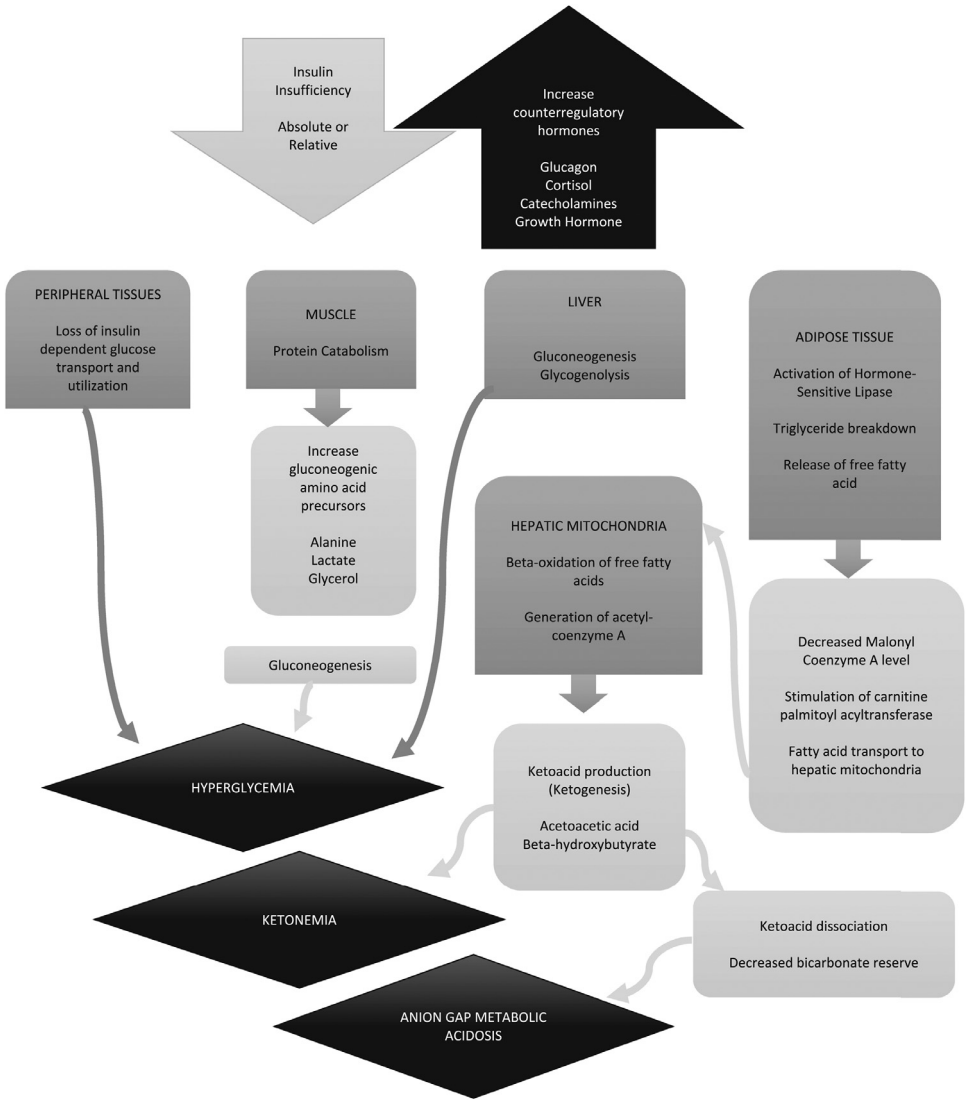

Fig. 1. DKA Pathophysiology diagram.

Diabulimia, an entity frequently described, occurs in patients with Type 1 diabetes who reduce their insulin doses or omit insulin completely for the purpose of weight loss. It is observed more in females with type 1 diabetes, who tend to have disturbed eating behaviors. Consequently, this decrease or omission in insulin dose leads to diabetic ketoacidosis in almost all cases and may be fatal.[27]

Clinical presentation

A good history and physical exam are the mainstays to diagnose DKA. Nausea, vomiting, abdominal pain, altered breathing, or progressive obtundation usually precipitate the visit to the emergency department. Polyuria, polydipsia, and polyphagia can be present along with a history of weakness, malaise, or lethargy.

On physical exam, patients exhibit signs of dehydration such as dry mucous membranes, tachycardia, and hypotension. Patients with significant metabolic acidosis tend to compensate with tachypnea and labored breathing to eliminate carbon dioxide. The high acetone levels cause the characteristic fruity odor in their breath. Mental status changes are also noted.[6]

Biochemical diagnosis

Although history and physical exam may suggest the diagnosis, a biochemical profile is still needed to diagnose DKA. The laboratory tests helpful in assessing the severity of illness and guiding treatment include a complete blood count, compre-

hensive metabolic panel, venous blood gas, and serum or urinary ketones, specifically beta-hydroxybutyrate. A sepsis workup may be needed if clinically indicated, and this includes blood cultures, urinalysis, urine culture, sputum culture, chest x-ray, or a CT scan. A glycated hemoglobin level is always useful.

Biochemical diagnostic criteria for DKA mainly comprise hyperglycemia, anion gap metabolic acidosis, and ketosis. In the US, the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and American College of Endocrinology (ACE) have published diagnostic classification criteria for DKA in adults and the Joint British Diabetes Societies published the UK National Guidelines for adults.[3] In pediatrics, the International Society of Pediatric and Adolescent Diabetes (ISPAD), as well as the British Society for Pediatric Endocrinology and Diabetes (BSPED), have similar definitions for the pediatric population, as shown in Table 1.[28,29]

The American Diabetes Association diagnostic criteria for DKA are the presence of hyperglycemia with blood glucose greater than 13.9 mmol/L (250 mg/dL), arterial pH less than or equal to 7.3, serum bicarbonate less than or equal to 18 mmol/L (mEq/L), blood anion gap greater than 10 mmol/L (mEq/L) and positive serum or urine ketone on a semi-quantitative test. However, they did not define a specific cutoff level for blood ketone concentration. On the other hand, according to the statement of the American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE), DKA is diagnosed with arterial pH less than 7.3, beta-hydroxybutyrate greater than or equal to 3.8 mmol/L (39 mg/dL), anion gap greater than 10 mmol/L (mEq/L), and hyperglycemia greater than 13.9 mmol/L (250 mg/dL) or lower glycemia in specific cases. From their statement, there was no specific cut-off for serum bicarbonate level.[3] In the UK, the diagnostic criteria consist of blood glucose greater than 11 mmol/L (200 mg/dL) or known diabetes, venous bicarbonate less than 15 mmol/L (mEq/L) and/or venous pH less than 7.3, and blood ketone greater than 3 mmol/L (31 mg/dL) or ketonuria more than 2+.[3,30]

According to the 2018 ISPAD clinical practice guideline, DKA is diagnosed with the biochemical triad of hyperglycemia defined as blood glucose greater than 11 mmol/L (200 mg/dL), venous pH less than 7.3 or serum bicarbonate less than 15 mmol/L (mEq/L), and ketonemia with blood beta-hydroxybutyrate greater than or equal to 3 mmol/L (31 mg/dL) or moderate or large ketonuria greater than or equal to 2+. (28) The 2020 BSPED interim guideline defines DKA as acidosis as evidenced by pH less than 7.3 or serum bicarbonate less than 15 mmol/L, with ketonemia of greater than 3 mmol/L (31 mg/dL) or ketonuria.[29]

Euglycemic DKA, does not conform to the conventional diagnostic criteria for DKA. According to Dhatariya et al, diagnosis of eDKA can be based on pH level, serum bicarbonate, and ketonemia. In the position statement of AACE and ACE, the diagnosis of DKA in patients taking SGLT-2 inhibitors is confirmed using arterial pH and serum beta-hydroxybutyrate levels. As for blood glucose levels in eDKA, there is no standardized definition. Munro et al first described eDKA in patients with blood glucose less than 16.7 mmol/L (300 mg/dL), whereas in more recent literature diagnostic criteria of eDKA include relative euglycemia with blood glucose less than 13.9 mmol/L (250 mg/dL). Biochemical criteria are also shown in Table 1.[1,6,17,31–33]

Patients with chronic kidney disease, more specifically those with end-stage kidney disease (ESKD) are another patient cohort that may not conform to the conventional diagnostic criteria for DKA. Patients with ESKD often are in a state of positive acid balance and may prove the diagnosis of DKA difficult. Galindo et al did a 10-year observational study to investigate the differences in biochemical parameters across the spectrum of patients with various degrees of kidney functions. They have noted that patients with end-stage kidney disease may present with lower beta-hydroxybutyrate levels while their bicarbonate and pH levels remain similar when compared with patients with preserved kidney function. It is important to note however that the study has inherent limitations such as a small sample size with only 49 patients comprising the ESKD cohort.[34]

Other laboratory findings

Water and electrolyte homeostasis disturbance

DKA causes water and electrolyte disturbances. Glucose, an extracellular solute, causes plasma hypertonicity which in turn promotes osmotic diuresis and natriuresis. This results in a net loss of electrolytes- sodium, potassium, calcium, magnesium, phosphate, and chloride.

The anion gap is a reflection of the difference between unmeasured anions and unmeasured cations. This is important to be determined in DKA because ketoacids that accumulate in this disease process are unmeasured anions. In DKA, use the measured, not corrected sodium concentration to calculate the anion gap. While we use the corrected sodium concentration to estimate the severity of dehydration in severe hyperglycemia.[35] It would also be important to mention that normally albumin accounts for the major unmeasured anion, this leads some to ask if we also need to correct for albumin levels in computing for the anion gap. In their observational study in 1998, Figge et al discussed the relationship between anion gap and albumin concentration. They did a simultaneous analysis of electrolytes and albumin levels in 152 critically ill patients and 9 healthy patients. They observed a very strong direct correlation (r=0.97) between serum albumin level and the difference between the anion gap and unmeasured gap anions. Based on this they surmised that for every 1 mg/dL difference in albumin, the anion gap should vary by 2.5 mmol/L (mEq/L) or simply for every 1 g/L increase/decrease in albumin, the anion gap is increased/decreased by 0.25 mmol/L. Their proposed formula for corrected anion gap (cAG) is as follows cAG (mmol/l) = anion gap + 0.25 × (normal albumin − measured albumin) (albumin is measured in g/l). This however was based on an equation for determining the charge for albumin in vitro and failed to account for in vivo factors.[36]

Table 1
Diagnostic and Classification Criteria for DKA ADA- American Diabetes Association, AACE- American Association of Clinical Endocrinologists/American College of Endocrinology, JBDS- Joint British Diabetes Societies, and ISPAD- International Society of Pediatric and Adolescent Diabetes (ISPAD)[1,3,6,17,28–31]

Diagnostic and Classification Criteria for DKA												
Age Group	Adult							Pediatric				
Criteria	ADA			AACE	JBDS		AACE	AACE	BSPED	ISPAD		
Classification	Mild	Moderate	Severe		Mild and Moderate	Severe	Euglycemic	Euglycemic		Mild	Moderate	Severe
Blood Glucose	>13.9 mmol/L or 250 mg/dL			>13.9 mmol/L or 250 mg/dL	>11 mmol/L or >200 mg/dL or known diabetes					>11 mmol/l or 200 mg/dL		
Arterial pH	7.25 to 7.30	7.00 to <7.24	< 7.00	< 7.3			<7.3					
Venous pH					<7.3	<7.0			<7.3	< 7.3	<7.2	<7.1
Anion Gap	>10	>12	>12	>10	>10 to 16	>16	>10	>10				
Serum bicarbonate	15 to 18 mmol/L	10 or <15 mmol/L	<10 mmol/L						<15 mmol/L	< 15 mmol/L	<10 mmol/L	<5 mmol/L
Beta Hydroxybutyrate				>or= 3.8 mmol/L	>or=3 mmol/L	>6 mmol/L	>or=3.8 mmol/L or 40 mg/dL	>or= 3.0 mmol/L or 31 mg/dL	>3 mmol/L	>or= 3.0 mmol/L		
Serum Ketone	Positive via Nitroprusside reaction method						Positive via Nitroprusside reaction method	Positive via Nitroprusside reaction method				
Urine Ketone	Positive via Nitroprusside reaction method				Positive via Nitroprusside reaction method					Moderate or Large, >or= 2+		
Mental Status	Alert	Alert to Drowsy	Stupor to Coma				Drowsy to Coma in moderate to severe DKA	Drowsy to Coma in moderate to severe DKA				

Table 2
Important Formulas used in diabetic ketoacidosis management[1,2,4]

Effective serum osmolality	Serum osmolality = (Serum sodium in mEq/L x 2) + serum glucose in mg/dL / 18 + serum urea in mg/dL / 2.8
Anion gap	Anion gap =(Na^+) – $[Cl^- + HCO_3^-$ (mEq/l)]
Sodium	Corrected sodium is computed by adding 1.6 mEq/L of sodium for every 100 mg/dL of glucose above 100 mg/dL or Corrected sodium = Measured sodium + 2 (plasma glucose in mg/dL – 100/100). or Corrected sodium = measured sodium + (plasma glucose in mmol/L -5.6)/3.5

According to the prospective study done by Hatherill et al in 2002 in children with shock, hypoalbuminemia is common in patients who are critically ill, and ailing to correct for albumin in computing for the anion gap may lead to missed diagnoses because of the failure to detect clinically significant amounts of lactate and other occult tissue anions.[37]

At this time, however, based on the different diagnostic criteria, the consensus for computing for the anion gap is not to correct for albumin. Anion gap is computed using the following formula: anion gap= (Na^+) – $[Cl^- + HCO_3^-$ (mEq/l)].[2] Computation of effective serum osmolality and anion gap can also be found in Table 2.

Hematologic changes

Elevated WBC count with left shift is often seen with DKA due to hypercortisolemia, elevated catecholamines, and acidosis. Leukocytosis may not necessarily indicate an acute infectious process. With leukocytosis greater than 25,000/uL, however, a full septic workup might be necessary.[2]

Classification

The severity of DKA for adults is classified by the American Diabetes Association (ADA) according to the degree of acidosis, bicarbonate level, and level of the sensorium, as shown in Table 1. DKA is classified as mild, moderate, and severe. Under the ADA severity classification, in patients with mild DKA, the patient would remain alert, has a pH of 7.25 to 7.30, a serum bicarbonate level of 15 to 18 mmol/L (mEq/L), and an anion gap greater than 10. Moderate DKA would be pH of 7.00 to less than 7.24, serum bicarbonate level of 10 to less than mmol/L (mEq/L), anion gap greater than 12, and mental alertness would be between alert to drowsy. Severe DKA is characterized by a patient that is stuporous to comatose and biochemical characteristics of pH of less than 7.00, serum bicarbonate level less than 10 mmol/L (mEq/L), and anion gap greater than 12.[2]

DKA severity for pediatric patients is defined by ISPAD as mild to moderate DKA with venous pH greater than or equal to 7.1 to less than 7.3 or serum bicarbonate greater than or equal to 5-15 mmol/L (mEq/L), and severe as pH less than 7.1, as shown in Table 1.[28]

Management

Treatment protocols may differ per institution, although the main goals of treatment of DKA remain the same. The optimal approach includes the resolution of dehydration, correcting hyperglycemia, ketosis, and acidosis, which goes hand in hand with judicious monitoring of the clinical signs and symptoms and laboratory results. Attempts to identify the precipitating cause and treatment are another cornerstone of DKA management. Individual response to interventions must also be considered hence individualization of treatment is also imperative.

According to the JBDS, management of DKA is aimed to achieve the following metabolic targets: Decrease in blood glucose by 3.0 mmol/L/hour (54 mg/dL/hour) and blood ketone concentration by 0.5 mmol/L/hour (5 mg/dL/hour), an increase of venous bicarbonate by 3.0 mmol/L/hour (mEq/L/hour), and lastly maintaining potassium concentration between 4.0- 5.0 mmol/L (mEq/L).[38] Available protocols rely on 3 major arms: intravenous hydration, insulin therapy, and electrolytes balance. A proposed algorithmic approach for the management of DKA is shown in Fig. 2.

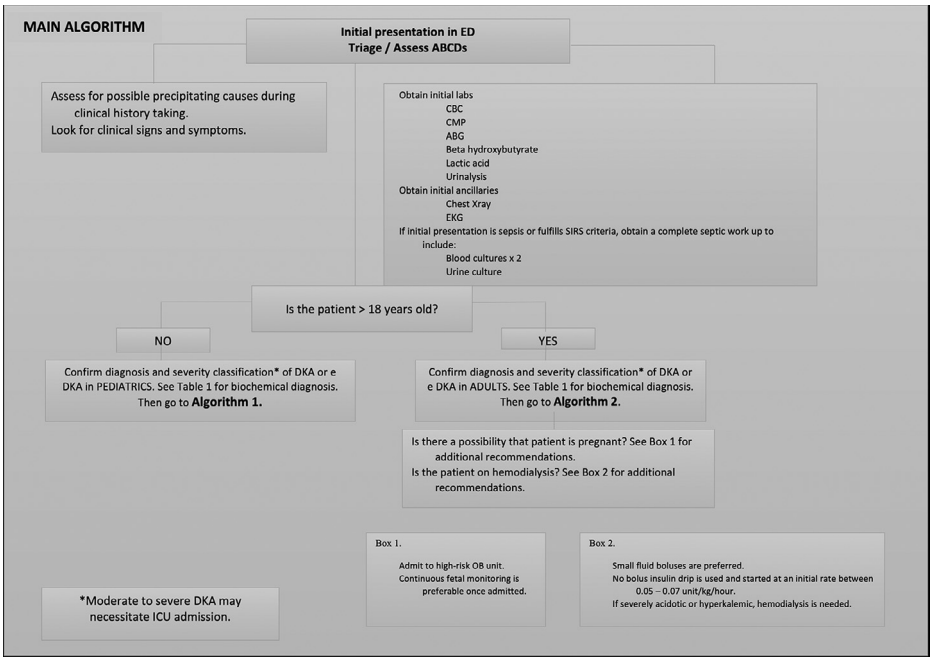

Fig. 2. Proposed Diabetic Ketoacidosis algorithm.

Resolution of intravascular volume depletion

(Fluid Resuscitation Regimen)

Adults

Fluid resuscitation does not only correct intravascular volume depletion but also improves renal perfusion and decreases the level of glucose and counter-regulatory hormones. Guidelines suggest that the total body water deficit for patients with DKA is between 5-and 8 liters. According to Umpierrez et al, the typical water deficit for adults is a 100 ml deficit per kg bodyweight which should be corrected within 24- 48 hours of diagnosis.[5]

Patients typically get 1 to 1.5L of crystalloid fluid or 20 ml/kg bolus during the first hour followed by maintenance fluid of 250-500 ml/hour or 4-14 ml/kg/hour. Additional boluses can be given depending on the patient's fluid status on reassessment. Crystalloid fluid in the form of 0.9 % Normal saline is the recommended initial fluid of choice. Several studies attempted to compare other balanced crystalloids such as Lactated ringers or Plasmalyte however benefits remain conflicting. The constitution of the maintenance fluid will depend upon the other electrolyte abnormalities specifically corrected sodium and serum glucose. Typically, 0.45% Normal saline is used except for hyponatremic patients where 0.9% Normal saline is advised. 5%-10% dextrose-containing fluids are used once serum blood glucose falls to 11-17 mmol/L (200-300 mg/dL). The specific level of blood glucose threshold of starting or adding dextrose to the fluid used for resuscitation is subjective or arbitrary depending on which guideline is used. Dextrose-containing fluid is continued to keep blood glucose between 8.4-14 mmol/L (150-250 mg/dL). This allows for the prevention of hypoglycemia with continued insulin infusion to correct the ketoacidosis as it takes longer to resolve.[1,2,5,6,12,30,39–41]

Fluid resuscitation should be carefully monitored in several patient populations such as the elderly, patients with heart failure, and end-stage kidney disease. In patients with end-stage kidney disease specifically those without residual kidney function, Galindo et al observed that treatment with fluid infusions- as suggested by current guidelines mentioned above- increased complications of fluid overload. This is attributed to the absence of osmotic diuresis in these patients resulting in increased extracellular fluid volume and causing volume overload and pulmonary edema. Hence fluid resuscitation must be individualized- history of fluid loss such as vomiting or diarrhea, the difference from dry weight, physical exam, and diagnostic imaging findings are to be considered. Volume status should be monitored frequently since this subset of patients is prone to develop fluid overload due to the absence of osmotic diuresis. If deemed euvolemic just starting insulin infusion without fluid boluses is suggested. If hypovolemic, small infusions or boluses of 250- 500 ml normal saline without maintenance fluid is recommended. In the event the patient is hypervolemic, hemodialysis is recommended.[42–45]

Pediatrics

Fluid resuscitation regimen in the pediatric population is also one area of DKA treatment that is controversial. For one, there is still no consensus as to the etiology of cerebral edema which is a more common complication in this population. The

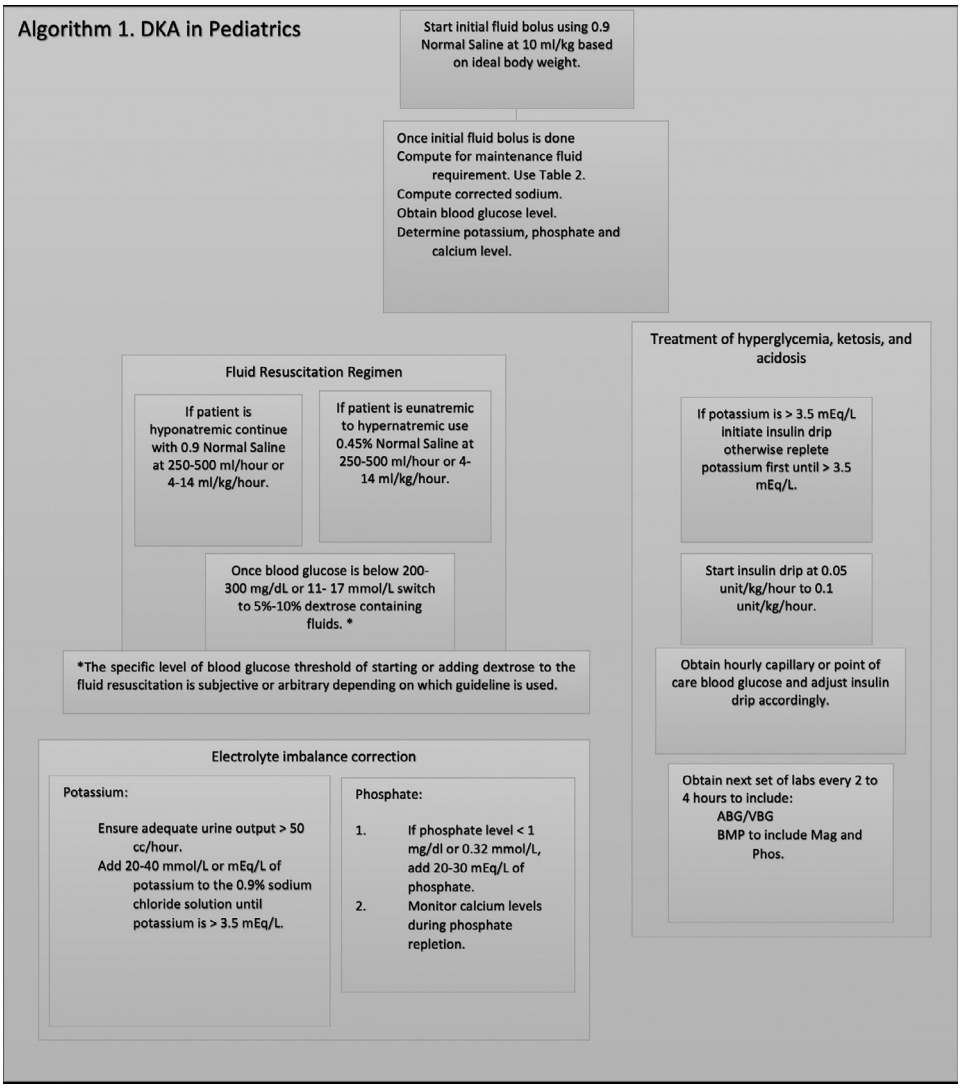

Fig. 2. Continued

one proposed association is the osmotic shifts from the rate of fluid or electrolyte replacement.[46] The Pediatric Emergency Care Applied Research Network (PECARN) FLUID study is a prospective randomized study across 13 centers comparing the acute and long-term neurological outcomes of giving rapid or slow fluid replacement using either 0.45% or 0.9% saline.[47] It did not show a significant difference between the different fluid protocols in terms of neurological outcomes.[23,30,31]

The British Society for Pediatric Endocrinology and Diabetes (BSPED) and the National Institute for Health and Care Excellence (NICE) advise the following: assume at least 5% dehydration level in pediatric patients who have mild-moderate DKA and at least 10% in severe DKA. As in the adult population, the first step is to start with fluid resuscitation and then initiate insulin administration. The initial fluid requirement is computed based on the ideal weight. During the first two hours of presentation, an isotonic crystalloid solution is initiated at 10 ml/kg.[24,32,33] Similarly, the consensus statement by Lawson Wilkins Pediatric Endocrine Society (LWPES), European Society for Pediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendation is also an initial bolus of 10 ml/kg to be infused over 30-60 mins. For those who are in shock, a fluid bolus equal to or greater than 20 ml/kg of isotonic saline can be administered. Shock is defined as poor peripheral pulses described as weak and thready and hypotension. A second bolus can also be administered for patients with severe dehydration. After the initial bolus, maintenance fluid of either 0.45% -0.9% NaCl or balanced salt solution such as Lactated ringer's, Hartmann's solution, or Plasmalyte can be utilized to replace the remaining fluid deficit over 24-48 hours. There are three suggested formulas to determine maintenance fluid requirements, they are as follows: Holiday- Segar formula, Simplified Holiday-Segar formula, and Body surface area-based

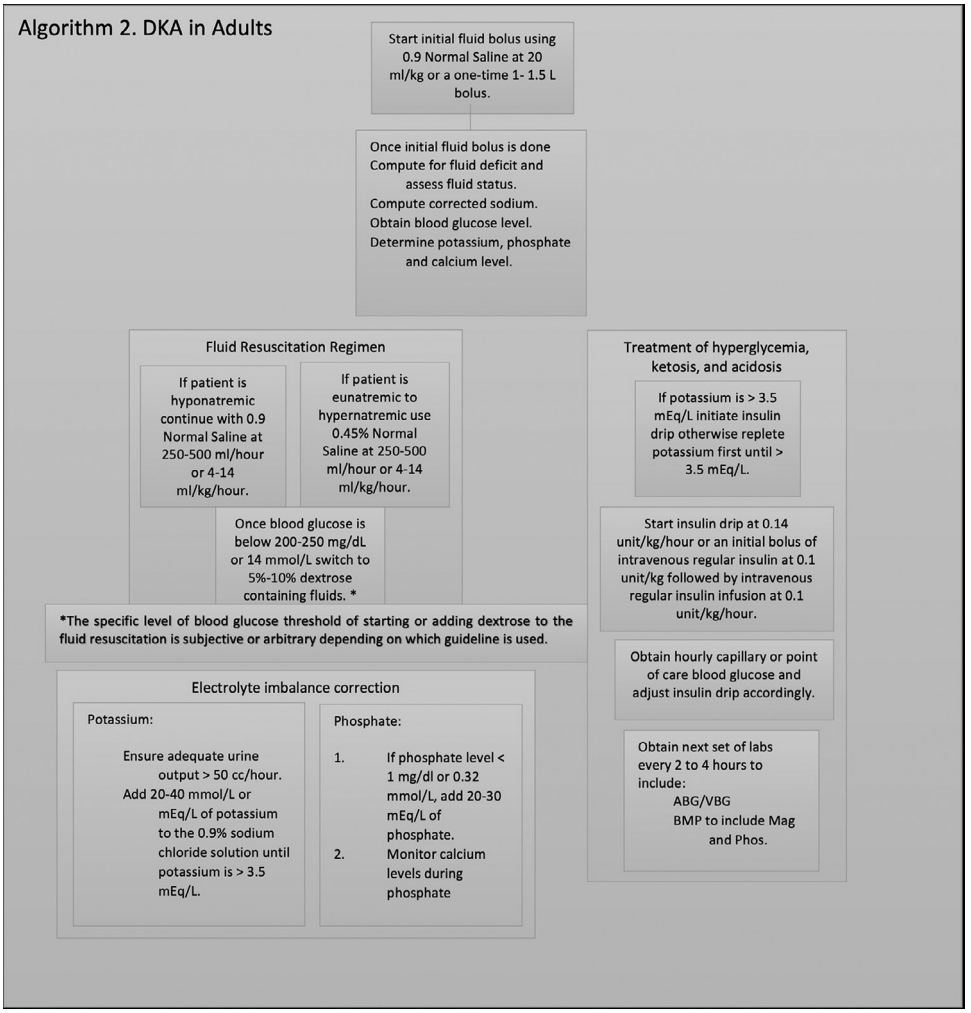

Fig. 2. Continued

formula. The Body surface area-based formula is utilized usually for patients weighing greater than 10 kg. See Table 3 for formulas/computations.[21,28,29,48–50]

Treatment of hyperglycemia, ketosis, and acidosis

(Insulin therapy)

Adult

Different institutions employ DKA algorithms with varying units/kg/hour, guidelines recommend that intravenous regular insulin is started at 0.14 unit/kg/hour or an initial bolus of intravenous regular insulin at 0.1 unit/kg followed by intravenous regular insulin infusion at 0.1 unit/kg/hour with the goal of reducing blood glucose by 10% during the first hour or 3.0 mmol/L/hour (54 mg/dL/hour). This is subsequently reduced to 0.02-0.05 unit/kg/hour and dextrose-containing fluid are started once blood glucose is at 11-17 mmol/L (200-300 mg/dL).[2,12] The JBDS also recommends using a fixed-dose insulin infusion at 0.1 unit/kg with the caveat that if the metabolic targets are not achieved then the infusion should be increased. JBDS team advises the use of long-acting insulin analogs such as Levemir and Lantus as it facilitates the easier transition to subcutaneous insulin, avoidance of rebound hyperglycemia, and ketogenesis, although the team agrees that there is no current evidence to base this recommendation.[30]

Several studies attempted to find alternative strategies for insulin regimens, one such study is a pilot study reporting the feasibility of coadministration of subcutaneous long-acting insulin glargine together with intravenous regular insulin infusion. Doshi et al performed a prospective randomized single-blind trial on a convenience sample of adult patients diagnosed with DKA. The control group was given intravenous regular insulin at 0.1 unit/kg/hour until the closure of the anion gap then given 0.3 units/kg insulin glargine; while the study group was given glargine 0.3 units/kg within 2 hours of diagnosis

Table 3
Methods for determining pediatric maintenance fluids[28,49,50]

Holiday-Segar formula		Simplified Holiday-Segar formula		Body surface area-based formula
Weight in kg	24-hour fluid maintenance requirement	Weight in kg	Hourly fluid maintenance requirement	1) Determine patient's body surface area, either by using a nomogram utilizing height and weight or estimating using Mosteller's formula of surface area in meter^2. BSA in m^2 is equivalent to the square root of weight in kilogram multiplied by height in centimeter divided by 3600. 2) The patient's fluid requirement is then estimated to be 1500 ml/m^2/day
Less than or equal to 10 kg	100 ml /kg/day	Less than or equal to 10 kg	4 ml/kg/hour	
11 to 20 kg	100 ml /kg/day for the first 10 kg then add 50 ml/kg/day for each kg above 10 kg or 1000 ml then add 50 ml/kg/day for each kg above 10 kg	11 to 20 kg	4 ml/kg/hour then add 2 ml/kg/hour for every kg above 10 kg Or 40 ml then add 2 ml/kg/hour for every kg above 10 kg	
Greater than 20 kg	100 ml /kg/day for the first 10 kg then add 50 ml/kg/day for each kg above 10 kg from 11 to 20 then add 20 ml/kg/day for each kg above 20 kg or 1500 ml then add 20 ml/kg/day for each kg above 20 kg	Greater than 20 kg	4 ml/kg/hour then add 2 ml/kg/hour for every kg above 10 kg from 11 to 20 then add 1 ml/kg/hour for each kg above 20 kg or 60 ml then add 1 ml/kg/hour for each kg above 20 kg	
Hourly maintenance fluid amount is then determined by dividing the total amount computed above by 24.				

and then started on an intravenous regular insulin infusion at 0.1 unit/kg/hour. The primary objective was to see if the coadministration of subcutaneous long-acting insulin glargine together with intravenous regular insulin infusion would decrease the time to resolution of ketoacidosis by determining the time to closure of the anion gap. The study concluded that the time to closure of the anion gap was similar between the two groups, as well as rates of ICU admissions, length of stay in the ICU, and incidence of hypoglycemia, suggesting that giving long-acting insulin earlier can be an alternative option. However, a clinical trial with a larger sample size is required to assess the efficacy of the regimen.[51]

In the case of eDKA, insulin infusion at 0.05 to 0.1 unit/kg/hour concurrently administered with 5% dextrose is recommended to resolve ketosis. If in the event the patient develops hypoglycemia on 5% dextrose, the recommendation is to use 10% dextrose.[52]

Patients with ESRD tend to present with higher levels of hyperglycemia but end up with more hypoglycemic episodes upon initiation of DKA treatment especially after dialysis (refer to specific population paragraph). Avoiding insulin bolus prior to starting the insulin infusion[40,45,53], initiating Insulin infusion at a lower dose (0.05 – 0.07 unit/kg/hour), and changing the rate and dose of insulin infusion to decrease blood glucose by 2.8-4.2 mmol/L/hour (50-75 mg/dl/hour) helps prevent hypoglycemia in this patient population.[45], These patients are not able to mount compensation for the metabolic acidosis and ketogenesis due to loss of renal function. Hemodialysis is the recommended approach for significant metabolic acidosis.[44]

Pediatric

Intravenous regular insulin is usually started 1-2 hours after fluid therapy with rates varying between 0.05 unit/kg/hour to 0.1 unit/kg/hour. This intravenous insulin infusion is continued until the acidosis resolves. When acidosis is still present and blood glucose drops below 16.8 mmol/L (300 mg/dL), the dextrose-containing fluid should be started.[14,23,24,30]

Determining whether the patient needs to be managed in the intensive care unit or on regular medical floors often depends on whether the patient is on intravenous insulin versus subcutaneous insulin.[6,41] Patients with mild DKA without underlying comorbid conditions may be treated with subcutaneous insulin on regular medical floors depending on the institutions, while those more severe and needing intravenous insulin are admitted to the ICU. Frequent monitoring is crucial no matter if the patient is in the ICU or not.

For both adults and pediatrics, the conversion to subcutaneous insulin is commenced when the patient is able to eat and the criteria for resolution of ketoacidosis are met. When transitioning to subcutaneous insulin, the recommended is to stop the insulin drip 2 hours after administering subcutaneous basal insulin to ensure adequate plasma insulin level to prevent the recurrence of ketogenesis and hyperglycemia. Subcutaneous insulin dosing depends on the prior use of insulin, patients who were previously well controlled on insulin they are resumed on the same home regimen while for patients who are insulin naive, weight-based dosing using between 0.5 to 0.8 units/kg/day is recommended.[2,12]

In some instances of ketoacidosis, intravenous bicarbonate is utilized to help expedite the correction of ketoacidosis. Several authors mention that the use of insulin to correct hyperglycemia is enough to correct ketosis and eventually acidosis. The ADA consensus guidelines, nonetheless, recommend that intravenous bicarbonate be considered in patients with severe acidosis whose venous pH is less than 6.9 who may decompensate without bicarbonate therapy, or patients who have bicarbonate levels less than 10 or pCO2 less than 12; because of known complications related to severe acidoses such as coma, cerebral vasodilation, impaired cardiac contractility, and gastrointestinal complications. The administration of intravenous bicarbonate entails its own complications such as hypokalemia, decreased oxygen uptake in tissues, paradoxical worsening of ketosis in adults, and cerebral edema in children. The recommended dose for intravenous bicarbonate is 100 mmol of sodium bicarbonate in 400 ml of sterile water with 20 mEq of potassium chloride, administered at 200 ml per hour for 2 hours until venous pH is greater than 7.0.[6,12,54] Prospective randomized studies performed on patients with venous pH greater than 7.0 have not shown any benefits in terms of the time of resolution of ketosis and acidosis, improvement of hemodynamic stability, or length of hospital stays.[6,54,55]

Electrolyte imbalance correction

Several electrolyte abnormalities are seen in diabetic ketoacidosis; hence electrolyte levels should be checked at least every 2-4 hours in the first 24 hours. The main electrolytes players are sodium and potassium. In adults, the total body deficit of sodium is between 7-10 mmol/L (mEq/L) and for potassium, it is around 3-5 mmol/L (mEq/L).[2,12]

On admission, patients with diabetic ketoacidosis may present with pseudo hyponatremia due to the excess extracellular water. Therefore, corrected serum sodium is usually computed to account for the level of hyperglycemia to determine the severity of sodium deficit as well as the fluid deficit. And as mentioned above, the constitution of the maintenance fluid in part depends on the corrected sodium, see Table 3 for computation.[1,12]

Potassium level is also monitored very closely in diabetic ketoacidosis, especially after the initial fluid resuscitation. If the potassium level is less than 3.5 mmol/L (mEq/L), it should be repleted first before initiating insulin infusion to avoid hypokalemia brought about by the intracellular shifting of potassium. However, before initiating potassium replacement the patient must be determined to have adequate urine output of greater than 50 ml/hour to ascertain kidney function. Consensus guidelines recommend adding 20-40 mmol/L (mEq/L) of potassium to the 0.9% sodium chloride solution once potassium levels fall below 3.5 to 5.5 mmol/L (mEq/L). Potassium replacement using a ratio of 2/3 potassium chloride and 1/3 potas-

sium phosphate is recommended by the ADA guideline while ISPAD has no preference for either form hence potassium chloride can be used alone.[1,2,4,26,30]

Patients with end-stage kidney disease usually present with higher potassium levels on admission as they are unable to excrete potassium. They must be continuously on cardiac monitoring. Insulin infusion promotes intracellular shifting of potassium if there is however clinical evidence of cardiac effects of hyperkalemia, emergent dialysis is needed.[44,45]

Phosphate deficiency similarly is also common in diabetic ketoacidosis since there is an extracellular shift due to the acidosis then it is eventually lost in the urine during osmotic diuresis. In patients with phosphate levels less than 0.32 mmol/L (1 mg/dl), adding 20-30 mEq/L of phosphate may be required. Phosphate replacement is also specifically indicated in patients who have anemia, respiratory and skeletal muscle weakness, and cardiac dysfunction. It is imperative however to monitor calcium levels when replacing phosphate to avoid tetany from hypocalcemia.[2,4,26]

Special populations

Several specific high-risk patient populations have been identified to require a tailored approach to management including pediatric, obstetric, chronic kidney disease, euglycemic DKA, and, more recently, COVID-19 patients.

Pediatric

Pediatric DKA at the time of diabetes diagnosis is more common in children who are less than five years old, who have a delay in diabetes diagnosis, and those who live in households with limited access to medical care.[56] The risk of DKA in children and adolescents with established type 1 diabetes is increased in children who miss insulin dosing, children on insulin pump therapy (an interruption in the pump will lead to insulin deficiency given that only rapid or short-acting insulin is in the pump), those who have poor metabolic control (high glycohemoglobin, high LDL, elevated blood pressure), those with a prior history of DKA, children with psychiatric disorders, and peripubertal patients.[56]

Fluid therapy is a crucial component of pediatric DKA management since this patient population commonly presents with significant volume depletion in the setting of osmotic diuresis and, oftentimes, vomiting. Given that a pediatric patient may be more difficult to obtain a history from, the duration of symptoms may be prolonged in these patients, which may lead to more severe dehydration and acidosis by the time the diagnosis of diabetes is made. Additionally, cerebral and autoregulatory mechanisms may not be well developed in the pediatric patient population.[56] The combination of increased illness severity at presentation with developing autoregulation puts these patients at higher risk for cerebral edema when compared to the adult patient in DKA.[56]

Unfortunately, cerebral edema, which occurs in 0.5-1% of all episodes of pediatric DKA, is the most common cause of death in pediatric patients who present in DKA.[56] Once cerebral edema occurs, there is a 20-25% risk of mortality.[56] Signs and symptoms of cerebral edema typically appear 4-12 hours after DKA treatment initiation and have occurred as late as 28 hours.[57] These may include recurrent vomiting, bradycardia, hypertension, decreased oxygen saturation, and change in neurological status such as posturing, abnormal pupillary response, cranial nerve palsies, restlessness, drowsiness, and incontinence.[56] Importantly, 40% of initial computed tomography scans will be unremarkable in pediatric DKA patient who shows signs of cerebral edema.[58] In the event of symptomatic cerebral edema, prompt fluid restriction and treatment with mannitol (up to 1mg/kg infusion) are recommended.[59]

The pathophysiology of cerebral edema in pediatric DKA is not well understood, but it is hypothesized that certain treatment approaches may cause or accelerate cerebral edema.[56] For instance, giving an intravenous insulin bolus prior to fluids may increase the risk of cerebral edema as it may lead to rapid changes in electrolytes.[60] Therefore, it is important to initiate regular insulin therapy after the patient has received fluid resuscitation with an isotonic solution at a rate of 10 mL/kg over 1-2 hours.[56] The intravenous fluid rate should be calculated based on a 5-7% deficit in ECF volume with rehydration to occur over 48 hours.[56] The daily maintenance fluid requirements can, thereafter, be calculated using several computations such as the Holliday-Segar formula.[61] Interestingly, a 2021 randomized controlled clinical trial showed no difference in cerebral injury in children with moderate or severe DKA who were rehydrated, after the initial resuscitation, with 0.45% saline or 0.9% saline. The administration of large volumes of fluid can be a risk factor for the development of cerebral edema, therefore, it is important to pay close attention to the neurologic status while rehydrating the pediatric patient who is in DKA.

Obstetric

Gestational DKA most often occurs in patients with type 1 DM, however, intractable vomiting and intrapartum steroid use may also trigger DKA in patients with type 2 DM or gestational diabetes mellitus (GDM). Notably, the most common precipitating factor is emesis. The incidence of DKA in pregnancy varies between 1%-10%, with an overall decrease in prevalence in recent years.[62] This downward trend is likely due to prenatal counseling with a focus on glucose control before pregnancy and an overall improved understanding of DKA management.

Adaptations in pregnancy can contribute to the development of DKA.[62] Pregnancy is a state of overall insulin resistance and decreased insulin sensitivity caused by hormones such as progesterone, prolactin, cortisol, human placental lactogen (HPL), and growth hormone (GH). Furthermore, increased minute ventilation in pregnancy results in a state of respiratory

alkalosis for which there is a secondary increase in bicarbonate excretion, thereafter, limiting the patient's ability to buffer ketone acids during DKA. While an infrequent complication of GDM, gestational DKA can be life-threatening to the mother and the fetus in the absence of prompt diagnosis and treatment.

Pregnancy does not alter the management of DKA. In their retrospective analysis of DKA in pregnancy, Baagar et al reported that the only factor associated with a favorable outcome is early gestational age at presentation.[63] Treatment involves aggressive fluid management, insulin, and management of the precipitating cause. With the correction of maternal hypovolemia and acidosis, fetal heart rate abnormalities during an episode of DKA will often resolve.[62] Therefore, the initial focus should be on stabilizing and treating the pregnant patient.

Chronic kidney disease

Diabetes mellitus is a major cause of end-stage kidney disease worldwide.[64] ESRD patients have decreased insulin clearance, lower insulin sensitivity, reduced renal gluconeogenesis, and reduced urine output or anuria.[65] Furthermore, difficulty with regulating volume, electrolytes, and acidemia places these patients at higher risk of complications in the setting of DKA. Altered physiology in this patient population requires a different approach to DKA management compared to non-ESRD patients.

DKA in patients with ESRD on HD should be suspected in the case of severe and persistent elevated anion gap metabolic acidosis.[66] DKA treatment in ESRD entails careful correction of electrolytes and judicious use of fluid and insulin. ESRD patients have delayed insulin clearance, placing them at risk of hypoglycemia. Adjustment of insulin infusion during and after hemodialysis should also be noted to avoid significant glucose variation and risk of hypoglycemia.[67] Fluid boluses should also be administered cautiously at smaller doses, such as 250 mL, and with close monitoring of fluid status to prevent pulmonary edema and cerebral edema.[68] Maintenance potassium is avoided as much as possible in this patient population. Typically, management and correction of acidosis are prioritized and if hypokalemia becomes evident then potassium supplementation is considered. Dialysis is recommended if hyperkalemia is intractable and associated with EKG changes.[68] Additionally, sodium bicarbonate is rarely of value in these patients due to the risk of hypernatremia, volume expansion, and increased osmotic pressure.[68] Due to the complex care needs of these patients, it is important to involve specialists such as nephrologists, endocrinologists, and intensivists early in the hospitalization.

Euglycemic DKA

eDKA is defined as a DKA with a blood glucose level less than 14 mmol/L (250 mg/dl). It most commonly occurs in patients who are in a low glucose state such as chronic liver disease, alcohol use disorder, starvation, pregnancy, and infection.[69] Sodium-glucose-cotransporter-2 (SGLT2) inhibitors, which cause increased urinary glucose exertion, have also been associated with eDKA. Thus, insulin resistance or reduced insulin secretion and low glucose availability predispose patients to ketogenesis and potentially eDKA.

As reported above, eDKA was first described in 1973 by Munro et al., followed by a larger case series in 1993.[70,71] The incidence of eDKA has increased over the years, specifically with the use of SGLT2 inhibitors. This class of medication has demonstrated efficacy in reducing blood glucose, hemoglobin A1c, body weight, blood pressure, and all-cause mortality, however, it has also been shown to increase the risk of eDKA by a factor of 7.[72,73,74] Patients on an SGLT2 inhibitor should be counseled on the importance of being evaluated for ketones in the setting of illness. The recommendation is to measure blood ketones more specifically beta-hydroxybutyrate, as the urine ketone test usually only measures acetoacetate levels and may be an inaccurate reflection of the level of ketosis.[17] If beta-hydroxybutyrate is present at levels $\geq$31 mg/dL (3.0 mmol/L) in children or $\geq$40 mg/dL (3.8 mmol/L) in adults, SGLT2 inhibitors should be withheld until ketosis resolves.[17,75] The half-life of an SGLT2 inhibitor is 11-13 hours and its effects can persist for a few days, therefore, this agent should be discontinued approximately 1-3 days prior to a surgical procedure, during periods of acute illness, or during intense physical activities to decrease the risk of developing eDKA.[17,76] In the setting of eDKA, SGLT2 inhibitors should be discontinued until the patient's condition is stable.[17,75]. The eventual resumption of SGLT2 inhibitors is recommended only in certain cases where another cause for eDKA is found and/or resolved.[38]

Management of this patient population includes resuscitation with intravenous fluids, insulin, glucose, and treatment of the precipitating event. In contrast to DKA management, since blood glucose in eDKA is less than 14 mmol/L (250 mg/dl), dextrose 5% should be added initially to the intravenous fluids to avoid hypoglycemia.[70] There should be a low threshold to increase glucose administration, via a higher percentage of dextrose, to correct severe acidosis and avoid hypoglycemia in eDKA.

COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) may precipitate DKA in patients with pre-existing diabetes whether previously diagnosed, newly diagnosed, or undiagnosed diabetes.[77] There have been several reports of DKA in COVID-19, however, the exact pathogenic mechanisms have yet to be determined.[78] There are several theories that SARS-CoV-2 binds to ACE2 in the pancreatic islet cells leading to islet cells damage with a secondary decline in insulin secretion.[79] This state of decreased insulin could trigger DKA, especially in patients with pre-existing DM. In addition,

interleukin-6, a cytokine of the inflammatory state in COVID-19, has been shown to promote ketogenesis.[80] Consequently, DKA may be more prevalent in COVID-19 in comparison to other infectious diseases.

Conservative fluid replacement and subcutaneous insulin regimen are practical and unique considerations in the management of DKA in patients with COVID-19.[1,78] Patients with DKA present with profound dehydration and fluid replacement is a critical part of treatment. However, in COVID-19, there are concerns that liberal fluid administration may cause pulmonary edema that would impair gas exchange. UK guidelines by the National Inpatient Diabetes COVID-19 Response Group recommend an initial bolus of 250 ml isotonic saline over 15 minutes followed by a weight-based infusion rate.[78,81] Notably, this conservative approach to fluid replacement can lead to delayed ketone clearance. It is also imperative to recognize that most patients with DKA present with a substantial potassium deficit, thus, stringent monitoring and management of serum potassium in these patients is advised.

Patients on intravenous insulin require ICU admission, infusion pumps, and frequent glucose monitoring. The COVID-19 pandemic has presented many challenges including limited resources and services in the inpatient setting. Therefore, the use of subcutaneous insulin therapy would allow for a reduction in ICU utilization and decreased exposure.[78] Several studies have shown that the use of subcutaneous rapid-acting insulin analogs is a safe and effective alternative in mild/moderate uncomplicated DKA.[78,82] Subcutaneous insulin is not recommended for patients with severe or complicated DKA. In addition, some of the medications used in COVID-19 treatment, such as corticosteroids and remdesivir, can also worsen hyperglycemia.[78,83] ISPAD has published a clinical practice consensus guideline for DKA and COVID-19 to utilize subcutaneous insulin for uncomplicated mild to moderate DKA in the pediatric population in the context of scarce ICU resources.[84] Thus, amid the ongoing pandemic, subcutaneous insulin therapy can be an effective means of treating DKA in a specific subset of patients with COVID-19.

Monitoring response to treatment

According to the ADA guidelines, the resolution criteria are blood glucose less than 11.2 mmol/L (200 mg/dL) and any two of the following criteria: venous pH greater than 7.3, an anion gap less than or equal to 12 mmol/L (mEq/L), serum bicarbonate level greater than or equal to 15 mmol/L (mEq/L). As for the JBDS guidelines, the criteria for resolution of DKA are pH greater than 7.3 and blood ketone concentration less than 0.6 mmol/L or less than 6.2 mg/dL.[20,21,34]

For pediatrics, per the ISPAD guidelines, the definition of resolution of DKA is pH greater than or equal to 7.30, serum bicarbonate greater than or equal to 15 mmol/L (mEq/L), beta-hydroxybutyrate less than 1 mmol/L (10 mg/dL), and/or closure of the anion gap.[28]

Prevention

To prevent DKA episodes, it is important to address the usual precipitating causes that we have mentioned in the previous section. Since infection is one of the most identifiable causes it is important to include sick day management for diabetic patients. Sick day management should include teaching patients and if possible, family members or caregivers to measure their blood sugar closely, adjusting insulin dose for patients on insulin or for patients on oral antihyperglycemics, measuring or checking for ketones in their urine, and more importantly when to contact their health care provider or providing them an emergency contact number.[6,12]

For patients who have insulin pumps and continuous glucose monitors, education should also include ways how to identify equipment failure and manage their diabetes with basal-bolus regimens when these technologies fail. They should also be provided with emergency numbers to call. It can be surmised hence that one of the most important parts of preventing DKA is proper patient education.

And lastly, we need to tackle the availability of medications specifically for patients who have limited access to healthcare or financial resources. Choosing the best insulin or oral antihyperglycemic regimen for patients is oftentimes influenced by cost and insurance coverage.[6] Prices of these medications vary from pharmacy to pharmacy and depending on the patient's insurance. And up to this time, even though insulin has been discovered decades ago, it is still inaccessible for most patients due to its high cost.

Conclusion

This was a comprehensive review of DKA where we tackled key points in understanding the pathophysiology of DKA and its management both in the adult and pediatric population. It aimed to integrate expert recommendations and consensus guidelines available for clinicians.

We must acknowledge that treatment of DKA must be individualized depending on patient-specific nuances. Consensus guidelines are meant to give generalized goals of treatment. We recognize that the optimal approach to treatment includes the following: the resolution of dehydration, correcting hyperglycemia, ketoacidosis, monitoring of the clinical signs and symptoms and laboratory results, and more importantly identifying the precipitating cause. It must also be acknowledged however that there are still areas specifically in management that have insufficient evidence and further outcomes-based studies need to be done with regards to insulin recommendations specifically the role of subcutaneous insulin, types of

fluid to be used for initial bolus and maintenance as well as the threshold for starting dextrose-based fluids, and utility of bicarbonate replacement.

What can be surmised from the available evidence at this time is that ultimately the prevention of patients going into DKA is of utmost importance. Through proper education, patient compliance, and the availability of medications such as insulin and oral antihyperglycemics.

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