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Diabetic Ketoacidosis in Type 2 Diabetes Mellitus Keeping an Eye

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Abstract

Diabetic ketoacidosis (DKA) is a life-threatening complication that occurs in patients with diabetes. Furthermore, to timely identification of the precipitating cause, the primary step in acute management of this disorder includes aggressive administration of intravenous (IV) fluids with appropriate replacement of electrolytes (primarily potassium), this is often always followed by administration of insulin, usually via an IV insulin infusion that's continued until resolution of ketonemia, but potentially via the subcutaneous (SC) route in mild cases. Common drawbacks in management include premature termination of IV insulin therapy and insufficient timing or dosing of SC insulin before discontinuation of IV insulin. This review encompasses recommendations for acute management of DKA, the complications associated with these disorders, and methods for preventing recurrence. It also talks about why many patients who present with these disorders are at high risk for hospital readmissions, early morbidity, and mortality well beyond the acute presentation.

Keywords: Diabetic Ketoacidosis; IV Fluids; Insulin; Electrolytes

Abbreviations: DKA: Diabetic ketoacidosis; SC: subcutaneous; IV: intravenous; FFA: Free fatty acids.

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening emergency that occur in patients with type 1 and type 2 diabetes. (1-4) DKA is defined by a triad of hyperglycemia (or a diagnosis of diabetes), metabolic acidosis, and ketonemia (Figure 1) [1-7]. Early diagnosis and management with focus on prevention strategies are essential to improve patient outcomes [1,2]. This is particularly important for patients presenting with "euglycemic" DKA, which is a term used to describe DKA which occurs simultaneously with lower than anticipated blood glucose values [1,5,7-9].

Criteria	ADA[1]	UK[2]	AACE/ACE[3]
Year of publication	2009	2013	2016
Plasma glucose concentration, mmol/L	>13.9 (250 mg/dL)*	>11 (>200 mg/dL)or known diabetes	NA
pH	Mild: 7.25-7.30; moderate: 7.00-7.24; severe: <7.00	<7.3 (severe: <7.0)	<7.3
Bicarbonate concentration, mmol/L or mEq/L	Mild: 15-18; moderate: 10-14.9; severe: <10	<15 (severe: <5)	NA
Anion gap: $Na^+-(Cl^-+HCO_3^-)$	Mild: >10; moderate: >12; severe: >12	NA (severe: >16)	>10
Urine acetoacetate (nitroprusside reaction)	Positive	Positive	Positive
Blood β-hydroxybutyrate, mmol/L	NA†	≥3 (31 mg/dL) (severe: >6)	≥3.8 (40 mg/dL)
Mental status	Mild: alert; moderate: alert or drowsy; severe: stupor or coma	NA	Drowsy, stupor, or coma

AACE/ACE=American Association of Clinical Endocrinologists/American College of Endocrinology; ADA=American Diabetes Association; NA=not included in guideline document.
*2019 ADA guideline provides update to this 2009 guideline and now states "There is considerable variability... ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma."[6]
†β-hydroxybutyrate updated to >3 mmol/L in 2016 updated review cited in 2019 ADA guideline.[6,7]

Epidemiology

The incidence of DKA has increased during the past decade, with more than 1,60, 000 hospital admissions in 2017 in the United States [10,11]. A recent analysis found that hospital admissions for DKA had increased in the United Kingdom for patients with both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) [12], DKA causes an approximate medical expenditure of $2.4bn (£1.9bn; €2.1bn) per year in the United States [9]. In the United Kingdom, the average cost for a single episode of DKA is estimated to be £2064 ($2682; €2384) per patient [13]. Diabetic ketoacidosis was a fatal disease before insulin was discovered in 1921. After nearly 100 years of insulin availability, mortality related to DKA in the adult population has progressively declined to less than 1% [11]. Certain patient groups have mortality rates of up to 5%, including patients with significant comorbid conditions and those with advanced ages [14]. There is renewed interest in euglyemic DKA, which was first described as a case series of 37 patients presenting with blood glucose levels below 300 mg/dL [8]. Euglycemic DKA can result in delayed diagnosis and treatment, as well as potential for adverse metabolic consequences [15]. Since the introduction of the SGLT2 inhibitors, several case reports and series describing euglycemic DKA in patients treated with these agents are published [16-18]. The entity of euglycemic DKA is not limited to patients using SGLT2 inhibitors, however, as it has also been described in the setting of alcohol use disorders, pregnancy, and chronic liver disease [8,19].

Pathophysiology

Diabetic ketoacidosis results from relative or absolute insulin deficiency alongside a rise in circulating concentrations of counterregulatory hormones (Figure 2) [1,20].

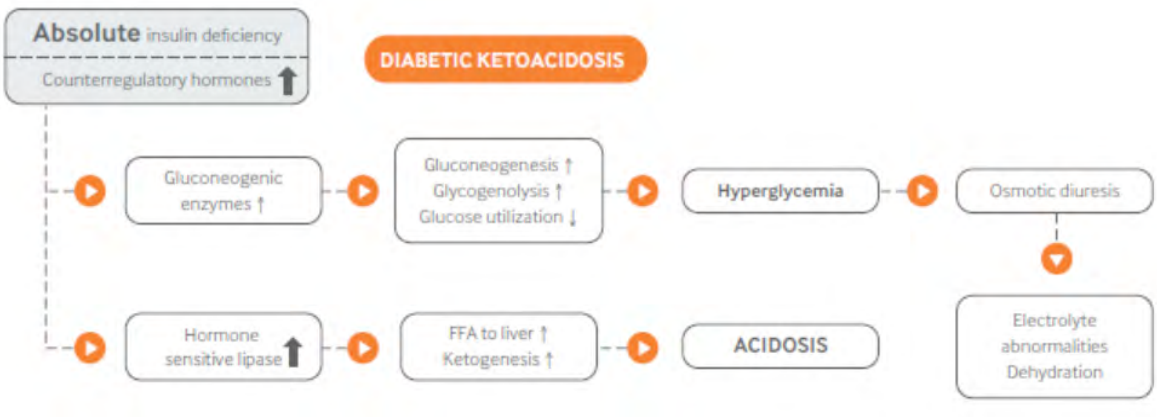

Figure 2: Pathogenesis of DKA.
(FFA: Free fatty acids)

Precipitating Causes

The most common precipitating factors in DKA are inadequate insulin therapy and infection, followed by new onset of diabetes and other metabolic stressors [21-23]. Certain drugs including glucocorticoids, excess diuretics, atypical antipsychotics, and others can predispose to severe hyperglycemia and DKA [24,25].

Precipitating Causes of DKA

In a large survey of 283 patients admitted to one of 72 hospitals in the United Kingdom, infection was identified as the most common precipitating factor for DKA (45%), followed by insulin omission (20%); other causes included newly diagnosed T2DMand alcohol or drug related abuse [26,27]. Insulin omission can be seen in patients of all ages and is more commonly observed in those with eating disorders, psychological distress, fear of hypoglycaemia or of weight gain [28]. Other factors that are associated with insulin omission include affordability , the idea that insulin should be withheld when illness interferes with eating, inadvertent omission of an insulin dose, and, rarely, pump malfunction [15,28,29]. It is not only patients who stop their insulin therapy. In the United Kingdom survey described above, more than 7% of cases of DKA occurred in an inpatient population [26]. Some healthcare providers also make false assumptions that patients over 50 years of age have T2DM and may tolerate periods of insulin omission when admitted to hospital for acute illness or surgical procedures, based on personal observations and experiences. Additionally, insulin therapy can be erroneously withheld or discontinued in patients admitted to the hospital with an insulin pump

device owing to a lack of familiarity with these devices on the part of hospital staff [30-32].

Sodium Glucose Linked Transporter-2 (SGLT2) inhibitors have been identified as causal agents in several reported cases of euglycemic DKA [18,33]. Risk factors for euglycemic DKA with SGLT2 inhibitors include latent autoimmune diabetes of adulthood, surgery, low carbohydrate diets, insulin withdrawal or dose reduction, and acute medical illness. Other clinical scenarios associated with euglycemic DKA include pregnancy, decreased caloric intake, heavy alcohol use, and chronic liver disease.

Clinical Presentation and Diagnosis

Diagnostic criteria for DKA can include an increase in urine acetoacetate or blood β-hydroxybutyrate. Point of care blood ketone meters and test strips for measurement of β-hydroxybutyrate are costly and not readily available in many institutions, but they're likely to become standard of care over time as they also provide accurate information for guiding treatment [34]. Patients with DKA can present with some or all the following symptoms: polyuria, polydipsia, nausea, vomiting, abdominal pain, visual disturbance, lethargy, altered sensorium, tachycardia, tachypnea, and Kussmaul respirations, with a fruity odour to the breath. Patients are usually severely volume depleted along with orthostatic hypotension. Patients with euglycemic DKA secondary to treatment with a SGLT2 inhibitor may have less polyuria and polydipsia owing to the milder degree of hyperglycemia and may instead present with malaise, anorexia, tachycardia, or tachypnea with or without fever [19].

Management of DKA

The goals of management of DKA include normalization of intravascular volume, prevention and/or correction of electrolyte abnormalities, correction of acidosis and hyperglycemia (if present) (Figure 3) [1,7,35].

Intravenous fluids

1 Use 0.9% sodium chloride solution (normal saline) for initial fluid replacement.
- ADA: 1000-1500 mL of normal saline during the first hour
- UK: 1000 mL of normal saline during the first hour

2 After the first hour, the rate of intravenous fluids should be adjusted on the basis of the patient's hemodynamic and electrolyte status and generally maintained between 250 and 500 mL/h
- ADA: Patients with a normal or high corrected sodium concentration can be switched to 0.45% sodium chloride after the first hour of fluid replacement
- UK: Normal saline should be continued throughout the management of DKA
- Insufficient evidence exists to support the hypothesis that balanced electrolyte solutions improve time to DKA resolution or prevent major adverse kidney events in this population

Note: Continued use of normal saline after the initial resuscitation may result in hyperchloremic metabolic acidosis and the inability to use plasma bicarbonate as a marker for DKA resolution

3 Add dextrose to the intravenous fluid if/when blood glucose approaches normal to allow continued insulin infusion at a rate sufficient to resolve DKA while avoiding hypoglycemia
- ADA: Add dextrose 5% when the blood glucose falls below 11 mmol/L (200 mg/dL)
- UK: Add dextrose 10% when the blood glucose falls below 14 mmol/L (250 mg/dL)
- A small randomized trial found no difference between 5% and 10% dextrose in DKA outcomes, but 10% dextrose caused more hyperglycemia[66]

Electrolytes

1 Patients with DKA have total body potassium deficits that must be replaced after adequate renal function (urine output) is assessed
- ADA: 20-30 mmol (20-30 mEq) potassium in each liter of infusion fluid when serum potassium is <5.2 mmol/L (<5.2 mEq/L)
- UK: 40 mmol (40 mEq) in each liter of normal saline when serum potassium is <5.5 mmol/L (<5.5 mEq/L)
- Evidence is lacking to support either recommendation over the other
- Note: Because insulin therapy promotes an intracellular shift of potassium, it is recommended that insulin should not be started if the serum potassium is <3 mmol/L (<3 mEq/L) to avoid worsening of hypokalemia

2 Routine replacement of phosphate or bicarbonate is not recommended (see text for details)

Insulin*

1 Intravenous insulin should not be started until after initiation of fluid resuscitation and correction of any hypokalemia
- ADA: Give intravenous insulin at either a fixed weight based dose of 0.14 units/kg/h or at a fixed weight based dose of 0.1 units/kg/h following a 0.1 units/kg bolus
- UK: Give intravenous regular insulin at a fixed weight based dose of 0.1 units/kg/h
- ADA recommendation is supported by a small randomized controlled trial[71]

2 Adjustment of intravenous insulin rate is needed to ensure resolution of DKA
- ADA: If plasma glucose does not decrease by 3-4 mmol/L/h (50-75 mg/dL) from the initial value in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved. When blood glucose is <11 mmol/L (<200 mg/dL), adjust dextrose or intravenous insulin rate to maintain blood glucose in the 8-11 mmol/L (150-200 mg/dL) range until DKA has resolved
- UK: Increase intravenous insulin rate hourly using direct measurement of β-hydroxybutyrate and increasing the insulin rate by 1 unit/h increments to achieve blood ketone reduction of at least 0.5 mmol/L/h (5.2 mg/dL/h); if blood β-hydroxybutyrate cannot be measured, increase insulin infusion rates by 1 unit/h to achieve increases of bicarbonate concentrations at a rate of ≥3.0 mmol/L/h (≥3 mEq/L/h) or decreases in blood glucose by ≥3 mmol/L/h (≥50 mg/dL/h)
- Evidence is lacking to support either recommendation over the other. Note: bicarbonate concentrations may not be reliable after the first 6 hours owing to the hyperchloremia resulting from continued use of normal saline

3 UK guidelines recommend continuing patients' usual basal insulin dose or starting weight based basal insulin during acute DKA management. In patients not previously treated with insulin, start basal insulin at a dose of 0.25-0.3 units/kg[74,75]

Identify/treat reason for DKA and prevent recurrence

See box 4

ADA=recommendations in the American Diabetes Association guideline[1]; UK=recommendation in the Joint British Diabetes Societies for Inpatient Care guideline[7]

*See box 2 for information about use of subcutaneous rapid acting insulin instead of intravenous insulin in selected patients with DKA

Figure 3: Principles of diabetic ketoacidosis management in adult patients.

Patients presenting with mild DKA who are alert and able to tolerate oral fluids may be able to receive treatment in the emergency department, potentially with oral fluids and subcutaneous insulin, and without need for hospital admission [36]. Patients presenting with more severe degrees of metabolic abnormalities need to be admitted to a hospital unit with trained staff and resources for intensive monitoring and administration of intravenous (IV) fluids, potassium, and insulin. The American Diabetes Association (ADA) and the Joint British Diabetes Societies for Inpatient Care have both published guidelines for management of DKA, but these guidelines have several differences. These differences are primarily due to lack of published evidence to guide treatment in many areas [35].

IV Fluids

Administration of fluid is the first line of treatment. Appropriate fluid administration not only restores intravascular volume but also lowers blood sugar, raises blood pressure (BP), ensures perfusion of peripheral tissues, and facilitates resolution of acidosis. Current ADA and UK guidelines for management of DKA in adults both recommend 0.9% sodium chloride solution (normal saline) for initial fluid replacement [1,2]. Specifically, the ADA recommends 1000-1500 mL, even the UK guideline recommends 1000 mL of normal saline during the primary hour. After the initial hour, the rate of IV fluids should be titrated based on the patient's electrolyte and haemodynamic status and generally maintained between 250 and 500 mL/h in adult patients without renal or cardiac compromise, advanced liver disease, or other states of fluid overload. The ADA guideline recommends that patients with a normal or high corrected sodium concentration can be switched to 0.45% sodium chloride after the first hour of fluid therapy. (1) However, the UK guideline recommends the continuation of normal saline throughout the management of DKA [2].

As glucose regularises with treatment, dextrose must be added to the IV fluid to allow continued insulin infusion at a rate enough to resolve ketonemia while avoiding hypoglycemia. The UK guideline recommends adding 10% dextrose when the blood glucose falls below 13.9 mmol/L (250 mg/dL) [2]. The ADA recommends adding 5% dextrose when the blood glucose falls below 11 mmol/L (200 mg/dL) [1].

Another strategy that has lately emerged is use of a "two bag method" for fluid replacement. This method consists of two bags of 0.45% sodium chloride, one with and one without 10% dextrose, that are adjusted based on hourly blood glucose monitoring to maintain an IV fluid rate of 250 mL/h. Two retrospective studies involving more than 500 patients found that the two-bag method was associated with earlier resolution of acidosis and shorter duration of IV insulin compared with conventional delivery of IV fluids [37,38]. When used in the emergency department, this method may reduce the need for hospital admission, and it may be associated with less hypoglycemia as compared with the conventional treatment.

Potassium Replacement

Patients with DKA have total body potassium deficit despite measured serum potassium concentrations that may be normal or even high at presentation. The ADA recommends adding 20-30 mEq potassium in each litre of infusion fluid when serum potassium is below 5.2 mEq/L [1]. In contrast to ADA guidelines, the UK guideline recommends 40 mmol/L in each litre of normal saline when serum potassium is below 5.5 mmol/L and the patient is passing urine [2]. Because insulin therapy promotes an intracellular shift of potassium, it is recommended that insulin should not be started if the serum potassium is below 3 mmol/L to avoid worsening of hypokalemia.

IV Insulin

The primary purpose of insulin in DKA management is to halt lipolysis and subsequent ketogenesis. Even patients with euglycemic DKA need adequate insulin therapy to correct ketonemia, albeit with early addition of fluids containing dextrose to prevent hypoglycaemia [19]. Insulin should not be started until after initiation of fluid resuscitation and correction of any hypokalemia to avoid worsening of volume or potassium deficits with shifting of potassium, glucose, and water from the extracellular to intracellular fluids compartment. The UK guideline recommends initiating IV regular insulin at a fixed weight-based dose of 0.1 units/kg/h [2]. The ADA guideline recommends initiating IV regular insulin at either a fixed weight-based dose of 0.14 units/kg/h or a fixed weight-based dose of 0.1 units/kg/h after a 0.1 units/kg bolus of IV insulin [1]. The ADA guideline states that reducing insulin infusion rates to 0.02-0.05 units/kg/h while dextrose 5% is added to the IV fluids may be possible when blood glucose declines to below 11 mmol/L (200 mg/dL) [1]. The UK guideline does not recommend any adjustment in the insulin rate when dextrose 10% is added after the blood glucose falls below 14 mmol/L (252 mg/dL) [2,39].

After insulin has been started, the ADA recommends increasing insulin infusion rates hourly to reduce blood glucose at a rate of 3-4 mmol/L/h (50-75 mg/dL/h) until concentrations of 8-11 mmol/L (150-200 mg/dL) are achieved [1]. On the other hand, the more recent UK guideline recommends using direct measurement of β-hydroxybutyrate (a hydroxy acid) and increasing the insulin rate by 1 unit/h increments to achieve blood ketone reduction of at least 0.5 mmol/L/h (5.2 mg/dL/h) [2].

Use of subcutaneous rapid acting insulin

An alternative to IV insulin therapy for acute management of mild to moderate DKA is the use of subcutaneous rapid acting insulin [40]. Potential candidate patients include those who are alert and do not otherwise need admission to a critical care area, have a pH above 7.0, and bicarbonate of at least 10 mmol/L (≥10 mEq/L) [41]. Four prospective randomized studies in adult patients with DKA compared subcutaneous rapid acting insulin (initial bolus of 0.3 units/kg followed by 0.1-0.2 units/kg every 1-2 hours) with conventional DKA treatment and found no difference in patient outcomes [41-44].

Phosphate Replacement

Patients with DKA also have total body phosphate deficits, but no prospective studies have shown that phosphate replacement improves outcome. The UK guideline recommends against routine phosphate replacement; checking and replacing phosphate should occur only if the patient has symptoms of respiratory and skeletal muscle weakness [2]. The ADA recommends that 20-30 mmol of phosphate may be indicated in patients with anemia, cardiac dysfunction, respiratory depression, or a phosphate concentration below 0.32 mmol/L (<1 mg/dL) [1].

Transition from Acute Management

After resolution of DKA (Figure 4), all patients need to be transitioned from IV to subcutaneous insulin [1,45]. This includes patients with euglycemic DKA secondary to treatment with an SGLT2 inhibitor and those with ketosis prone diabetes who present with DKA. To prevent rebound ketoacidosis or hyperglycemia, administration of a long acting basal insulin (if this has not already been given in the previous 24 hours) with or without a short or rapid acting insulin is needed at least two hours before the IV insulin infusion is stopped [45-47]. The ADA and UK guidelines recommend that patients previously treated with subcutaneous insulin can be restarted on their pre-admission insulin doses if these are determined to be appropriate [1,2]. Otherwise, a weight based subcutaneous insulin regimen can be started by calculating a total dose of 0.5-0.7 units/kg/d and giving 50% of the total dose as once daily basal insulin and dividing the other 50% equally between pre-breakfast, pre-lunch, and pre-supper doses of rapid acting insulin [1,2,7].

Criteria	ADA[1]	UK[2,4]
Resolution of DKA	Blood glucose <11 mmol/L (200 mg/dL) PLUS any two of bicarbonate ≥15, pH >7.3, and anion gap ≤12	pH >7.3 AND blood ketone concentration <0.6 mmol/L (<6.2 mg/dL). Bicarbonate not recommended because hyperchloremic acidosis is associated with large volumes of 0.9% sodium chloride solution

Figure 4: Criteria for resolution of DKA.

Complications Related to Management of DKA

Cerebral Edema

Of these complications, the development of cerebral edema is the most serious [48,49]. This has been described most commonly in young children and adolescents presenting with DKA as the initial manifestation of new onset type 1 diabetes, but it has also been described in young adults up to age 28. [49,50]. Rare cases of cerebral edema occur in adults over age 28, but current recommendations suggest maintaining blood glucose concentration no lower than 13.9-16.6 mmol/L (250-300 mg/dL) for several hours during treatment for patients with either DKA or HHS as a potential method for avoiding this devastating complication [1,2,7].

Early recognition of potential neurologic deterioration such as new onset or intensifying headache, a decline in level of consciousness, recurrent vomiting, incontinence, irritability, abnormal respirations, or evidence of cranial nerve dysfunction provide suggestive evidence of onset of cerebral edema. Prompt administration of mannitol therapy administered at a dose of 0.5-1 g/kg over 20 minutes can help to abort further neurologic deterioration [51].

Electrolyte Aabnormalities

More commonly observed complications in adults include hypokalemia and hyperkalemia, hypoglycemia, and non-anion gap hyperchloremic metabolic acidosis [26,45,52]. Hypokalemia is reported more frequently than hyperkalemia and usually results from delays in administration of or insufficient potassium containing supplementation. Hyperkalemia can result from overly aggressive potassium replacement, particularly in patients with underlying renal dysfunction [45,53]. Hypoglycemia can result from overly aggressive insulin infusions, insufficient frequency of blood glucose monitoring, or failure to add dextrose to IV fluids when blood glucose concentrations approach 13.9 mmol/L (250 mg/dL) [52,53].

The development of non-anion gap hyperchloremic metabolic

acidosis often follows the acute phase of DKA management [1,54,55]. This has been attributed to administration of large volumes of IV fluids containing normal saline during acute DKA management, as well as to urinary losses of keto-anions that are needed for regeneration of bicarbonate.

Cardiac, Respiratory and Muscle Complications

Other complications that occur less frequently but for which monitoring is important include myocardial infarction, potential for pulmonary edema in patients with underlying congestive heart failure, and rhabdomyolysis in patients who present with more severe degrees of dehydration [56]. In one recent study of 3572 patients with T2DMand 7144 controls matched for age, sex and baseline diabetes complications and comorbidities, patients with DKA were 1.55 times more like to experience a stroke within six months than were those without DKA [57]. In another study examining long term outcomes inpatients admitted to a care unit with DKA, one in 10 patients died within one year of hospital discharge [58]. The average age of patients in this report was 38 years, suggesting that these patients represent a group for whom a heightened degree of surveillance with associated interventions is needed to offset the mortality risk.

Emerging Treatments

Several studies are investigating better treatment strategies with insulin and IV fluids, as well as alternative treatment strategies and previously unexplored adverse outcomes in adult patients presenting with decompensated diabetes. Some of these trials are listed below.

Clinicaltrials.gov NCT02930044

The purpose of this study is to determine whether adult patients with DKA who present to the emergency department and are treated with glargine insulin (0.3 units/ kg with a maximum dose of 30 units) within two hours after starting the IV insulin infusion need a shorter duration of IV insulin administration to resolve DKA compared with standard care (insulin glargine administered two to three hours before stopping IV insulin).

Clinicaltrials.gov NCT03717896

The purposes of this randomized, double blind, placebo controlled trial are to determine whether administration of IV thiamine (200 mg in normal saline twice daily for two days) will lead to quicker resolution of acidosis in patients with DKA and to investigate whether thiamine improves cellular oxygen consumption, shortens length of stay in hospital, or decreases resource use. This novel study is based on preliminary studies from the investigators showing that thiamine concentrations, which are deficient in up to 37% of patients with DKA, are inversely associated with the severity of acidosis. It is scheduled to be completed in 2023.

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