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Clinical Reviews

Alcoholic Ketoacidosis: Etiologies, Evaluation, and Management

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☐ **Abstract—Background: Alcoholic ketoacidosis (AKA) is defined by metabolic acidosis and ketosis in a patient with alcohol use. This is a common presentation in the emergency department (ED) and requires targeted therapies. Objective: This narrative review evaluates the pathogenesis, diagnosis, and management of AKA for emergency clinicians. Discussion: AKA is frequently evaluated and managed in the ED. The underlying pathophysiology is related to poor glycogen stores and elevated nicotinamide adenine dinucleotide and hydrogen. This results in metabolic acidosis with elevated beta-hydroxybutyrate levels. Patients with AKA most commonly present with a history of alcohol use (acute or chronic), poor oral intake, gastrointestinal symptoms, and ketoacidosis on laboratory assessment. Patients are generally dehydrated, and serum glucose can be low, normal, or mildly elevated. An anion gap metabolic acidosis with ketosis and electrolyte abnormalities are usually present on laboratory evaluation. Management includes fluid resuscitation, glucose and vitamin supplementation, electrolyte repletion, and evaluation for other conditions. Conclusions: Emergency clinician knowledge of the evaluation and management of AKA is essential in caring for these patients. Published by Elsevier Inc.**

☐ **Keywords—alcoholic ketoacidosis; alcohol; malnutrition; acidosis**

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Clinical Scenario

A 45-year-old man presents to the emergency department (ED) with nausea, vomiting, and diffuse abdominal pain. He states that he regularly uses alcohol but discontinued use 1 day ago, as he was unable to obtain alcohol. His vital signs are normal except for a heart rate of 110 beats/min and respiratory rate of 22 breaths/min. Examination reveals diffuse abdominal tenderness but no evidence of peritonitis. His electrolytes include a glucose of 72 mg/dL, serum sodium of 136 mEq/L, and serum chloride of 100 mEq/L. His venous blood gas reveals a serum pH of 7.20 and bicarbonate of 16 mEq/L.

Introduction

Background

Alcoholic ketoacidosis (AKA) is a syndrome defined by alcohol use and ketoacidosis. It is most commonly found in those with chronic alcohol use but can be seen in patients with binge drinking (1–4). The disease was first described in 1940 by Dillon et al., detailing the case of 9 patients with ketoacidosis and chronic alcohol use

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without diabetes (5). Subsequent case reports of AKA described patients with a history of chronic heavy alcohol use who had ceased drinking, followed by the onset of severe nausea, vomiting, and abdominal pain with associated ketoacidosis (6–9). As the literature has evolved, there is a growing evidence base on this important condition with potential morbidity and mortality. Therefore, it is critical for emergency clinicians to be aware of the diagnosis and management of this condition.

Methods

This narrative review will characterize AKA and provide updates in the evaluation and management for the emergency clinician. The authors searched PubMed and Google Scholar for articles using the keywords "alcoholic ketoacidosis." The search was conducted from the database inception to February 24, 2021. PubMed yielded 178 articles. The authors evaluated case reports and series, retrospective and prospective studies, randomized controlled trials, systematic reviews and meta-analyses, and other narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. The literature search was restricted to studies published in English, with a focus on the emergency medicine and critical care literature. Authors decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 37 resources were selected for inclusion in this narrative review by author consensus.

Discussion

Epidemiology

According to the 2019 National Survey of Drug Use and Health, approximately 15 million patients over age 12 years have alcohol use disorder (AUD), defined by impaired ability to control or stop alcohol use despite adverse health, occupational, and social consequences (10). Men account for 9 million of these patients with AUD, and 414,000 patients are between the ages of 12 and 17 years. Unfortunately, only 7.2% of these patients with AUD received treatment in the past year (10). Determining the epidemiology of AKA is challenging given its variable presentation and likely underdiagnosis. The prevalence of AKA varies depending upon the setting, with higher rates of AKA in communities with higher incidences of alcohol abuse. Current studies demonstrate an equal incidence of AKA in men and women (1–3,8). One study suggested higher rates of AKA among patients with slow-metabolizing alcohol dehydrogenase enzymes, who drink whiskey, have baseline hypoglycemia, have lower body mass indices, or smoke (11). Literature suggests that AKA may be associated with increased risk of mortality, with AKA accounting for 7% of deaths in patients with alcohol use (12,13).

Pathophysiology

The pathophysiology of AKA is complex and related to the underlying effects of alcohol within the body. There are several primary components: reduced glycogen and nutritional stores, elevation of the reduced form of nicotinamide adenine dinucleotide and hydrogen (NADH) when compared with NAD+, and volume depletion (1–4).

Patients with chronic alcohol use often experience poor dietary intake with reduced nutritive value (2,3,14,15). This induces a starvation state with decreased insulin secretion and increased production of glucagon, growth hormone, cortisol, and catecholamines. These hormones result in depression of gluconeogenesis and glycogenolysis, decreasing glucose availability (2,16–18). Hormone-sensitive lipase also increases with reduced insulin, which results in up-regulation of lipolysis and release of free fatty acids from adipose tissue. These free fatty acids are oxidized to carbon dioxide or ketone bodies or esterified to phospholipid and triacylglycerol. Free fatty acids are normally transported to the mitochondria by carnitine acyltransferase, but in the setting of AKA with reduced insulin-to-glucagon ratio, the body cannot shunt fatty acids to the mitochondria via carnitine acyltransferase, resulting in oxidation of free fatty acids and ketone body production (2,16–22).

Metabolism of alcohol itself contributes to reduced glucose availability and ketosis. Alcohol dehydrogenase metabolizes alcohol to acetaldehyde in the liver, which is metabolized further to acetic acid in mitochondria. These steps require reduction of NAD+ to NADH. This consumes NAD+ and generates NADH. The elevated NADH/NAD+ ratio has several implications. First, conversion of lactate to pyruvate is impaired, increasing lactic acid levels in the serum (1,2,14,17–22). Second, gluconeogenesis is impaired because pyruvate and other substrates such as thiamine are depleted and not available for glucose production. Third, there is an increase in beta-hydroxybutyrate to acetoacetate production in ratios higher than even diabetic ketoacidosis (19:1 vs 11:1) (1,2,14,17,18). Thus, elevated NADH interferes with mitochondrial activity, suppresses gluconeogenesis, increases lipid metabolism to ketoacids, increases conversion of acetoacetic acid to beta-hydroxybutyric acid, and increases conversion of pyruvate to lactate (1,2,17–22).

Alcohol is also associated with volume depletion due to poor oral intake and vomiting. Although not all patients with AKA present with vomiting, the majority will experience protracted vomiting. Alcohol also directly inhibits antidiuretic hormone secretion, decreasing free water reabsorption. These factors decrease renal perfusion, reducing ketoacid urinary excretion, and also increase counter-regulatory hormone concentration, further increasing lipolysis and ketone body production (1,2,7,14,18,22). Thus, reduced glycogen stores, increased NADH, and volume depletion all result in AKA with anion gap metabolic acidosis, ketosis, and reduced glucose availability (1–3,14–22).

Etiology

The majority of cases of AKA occur in a patient with poor nutritional status associated with long-standing alcohol use or a drinking binge accompanied by sudden decreased oral intake (1–4,6). Infection and pancreatitis are common precipitants of AKA, but other factors that can reduce oral intake should be considered, including intra-abdominal pathology (e.g., cholecystitis, appendicitis, obstruction, perforation, mesenteric ischemia), alcohol withdrawal, diabetic ketoacidosis, and other toxic ingestion (e.g., salicylate toxicity) (1–4).

History and Physical Examination

The most common presentation of AKA is a patient with a history of alcohol use, poor nutrition, and cessation of drinking with the development of gastrointestinal symptoms (1,3,4). The most frequent symptoms include nausea (up to 76%), vomiting (up to 73%), and abdominal pain (40–75%) (1–4,6–8,18,21). These symptoms typically occur prior to the development of ketoacidosis (1–4). Patients also frequently present with evidence of volume depletion. Tachypnea, tachycardia, hypothermia, and hypotension are common, though there are no clear data providing exact numbers. Diffuse abdominal tenderness can be present in up to 75% of patients (1,3,8). Abnormal bowel sounds, abdominal distension, and rebound tenderness are not common and suggest another intra-abdominal condition (3). Patients are typically alert with normal mental status, despite the ketoacidosis (1–3,9). Other presenting signs and symptoms described in patients with AKA include tremulousness, dizziness, myalgias, diarrhea, seizure, and syncope (1–4,6) (Table 1). Nystagmus/oculomotor dysfunction, dysmetria, incoordination/ataxia, memory impairment, or altered mental status should not be present in isolated AKA (23,24). These signs should prompt consideration of Wernicke encephalopathy (23,24).

Laboratory Evaluation

Laboratory evaluation should include a venous blood gas, ketone body assessment, renal function, liver function, and electrolytes. One of the primary defining factors is an anion gap metabolic acidosis with ketosis (1–3). As discussed, the anion gap metabolic acidosis is the result of lactate and ketone body accumulation, predominantly consisting of beta-hydroxybutyrate rather than acetoacetate (1–3,9). Severe lactic acidosis (lactate $>$ 4 mmol/L) is not common in AKA and suggests another concomitant condition such as sepsis, impaired liver function, thiamine deficiency, or seizures (9). Importantly, patients with AKA may have mixed acid-base disorders. One study found only 23% of patients with AKA had an anion gap metabolic acidosis alone (1). Mixed anion gap metabolic acidosis with respiratory alkalosis was present in 25% of patients. Metabolic alkalosis with metabolic acidosis and respiratory alkalosis was present in 28%, likely due to vomiting and tachypnea (which can be due to pain or concomitant respiratory causes, including infections). Finally, 15% had mixed anion gap metabolic acidosis with hyperchloremic metabolic acidosis (1).

Due to the complex nature of AKA and possibility of multiple acid base disorders, several calculations are recommended. A mixed acid-base disturbance can be detected by calculating an anion gap, followed by use of Winter's formula and the delta-delta gap (25). The anion gap is calculated to determine whether the acidosis is gap vs. non-gap. It is calculated by adding the serum chloride and bicarbonate and then subtracting this number from the serum sodium. The normal anion gap will vary based on the respective laboratory's reference range, but is normally between 3 and 12 mmol/L (25). Winter's formula utilizes serum bicarbonate to determine the level of compensation in a patient with metabolic acidosis, calculated by $1.5 \times [HCO^{3-}] + 8$. This provides the partial pressure of carbon dioxide (pCO_2). Values above or below the expected pCO_2 level suggest a concomitant respiratory acidosis or respiratory alkalosis, respectively. The delta-delta is calculated as: Δ anion gap $-$ Δ serum bicarbonate (25,26). This is the deviation from a normal anion gap subtracted by the deviation from a normal serum bicarbonate from their normal reference ranges. In a pure high anion gap ketoacidosis, there is a near equal ($\pm$5) rise in the anion gap and decrease in the serum bicarbonate (25,26). Any deviation from the expected delta-delta gap $>$ 5 in ketoacidosis suggests a mixed-acid base disorder (25). A delta-delta $>$ 5 suggests a high anion-gap metabolic acidosis in addition to a metabolic alkalosis, whereas a delta-delta $<$ $-$5 suggests a high anion-gap plus a non-anion gap metabolic acidosis (25). For instance, it is possible that a metabolic alkalosis from gastric fluid losses associated with vomiting and dehydration may

Table 1. Key Features in the History and Examination of Patients with AKA

History:
Chronic alcohol use or recent binge with little to no other oral intake
Cessation of alcohol intake followed by nausea, vomiting, or abdominal pain
History of recurrent similar episodes
Examination:
Volume depletion with tachycardia, hypotension, increased respiratory rate
Nausea, vomiting, and abdominal tenderness; not typically peritoneal or localized
Mental status may be mildly altered but is typically normal

AKA = alcoholic ketoacidosis.

approximate the high anion gap metabolic acidosis of the ketoacidosis. Therefore, AKA can be challenging to diagnose in those with mixed acid-base disorder, as the serum bicarbonate may be higher than expected if there is an additional acute or chronic metabolic alkalosis (e.g., gastric losses from vomiting, reduced oral intake, metabolic compensation for a chronic hypercapnic respiratory failure).

The diagnosis of ketosis includes detection of ketone bodies within the serum or urine. Ketone testing utilizing nitroprusside primarily detects acetoacetate and does not react with beta-hydroxybutyrate, the predominant ketone body in AKA (1–4,9,22). Therefore, urine ketones may be low to moderate in AKA, or may even be falsely negative. If urine ketone assessment is negative, serum beta-hydroxybutyrate levels should be obtained. In AKA, serum beta-hydroxybutyrate levels are elevated and typically range from 5.2 mmol/L to 14.2 mmol/L (3,22). Classically, serum alcohol levels are low or undetectable (1–3,6–8). However, serum alcohol levels may be elevated in patients with chronic alcohol use. One study found that 80% of patients with AKA had alcohol levels over > 100 mg/dL (4). Although toxic alcohols (e.g., methanol, ethylene glycol) should be considered in a patient with an anion gap metabolic acidosis, they should not cause ketosis. Ethylene glycol and methanol toxicity should be considered in patients with severe anion gap lactic acidosis (serum bicarbonate < 10 mEq/L, pH < 7, lactate > 4 mmol/L) or elevated osmolal gap, as well as those with altered mental status and severe end organ injury (e.g., cardiopulmonary, renal) (27). Table 2 demonstrates conditions associated with ketoacidosis and anion gap acidosis (3,23,24,26,28,29).

Serum glucose levels are most commonly low or normal, but they may be elevated (1–3). If glucose levels are elevated, they are typically < 275 mg/dL (1,9,16). One study found that 12% of non-diabetic patients with AKA had a serum glucose level < 60 mg/dL, whereas 11% had a serum glucose level > 250 mg/dL (1). Despite this, serum glucose levels > 250 mg/dL should prompt consideration of diabetic ketoacidosis, as the majority of patients with AKA will have low or normal serum glucose levels (9,16,26). Chronic alcohol use in the setting of AKA can result in several electrolyte disorders due to decreased nutrition and oral intake, as well as urinary losses (1–4,18). Hyponatremia may be present due to vomiting and extracellular volume loss. Total body potassium is generally low due to gastrointestinal and renal losses, as well as overall poor nutrition (1–4,18). Hypomagnesemia can occur in approximately 20% of patients with AKA, and chronic alcohol ingestion may result in increased renal magnesium excretion (1–3,18,30). However, serum magnesium levels are not reliable measures of total body magnesium stores, and hypokalemia functions as a strong indicator of hypomagnesemia due to linked excretion of potassium and magnesium. Total body phosphate depletion is also common due to poor oral intake and nutrition, as well as vomiting and enhanced urinary excretion due to alcohol (1–4,18). Despite a low total body level, serum phosphate levels may be normal or even elevated due to the metabolic acidosis and low insulin levels (1–3,6,8). Hypophosphatemia is not typically uncovered until treatment is initiated with glucose and fluid resuscitation (1–3,6,8). Patients are not typically symptomatic from hypophosphatemia until levels are < 1 mg/dL. An elevated osmolal gap may be encountered due to increased serum acetone levels, with a mean of 27 mOsmol/kg in one study (29). Other laboratory findings include elevated blood urea nitrogen and creatinine due to dehydration and mild elevation of liver enzymes (1,3).

Management

Patients with AKA require fluid resuscitation and repletion of glucose and electrolytes, along with symptomatic therapy (i.e., antiemetics). Any underlying etiology such as sepsis or intra-abdominal pathology must be managed appropriately (3). Intravenous resuscitation with balanced fluids (e.g., PlasmaLyte, lactated Ringers [LR]) or normal saline is recommended in the initial stages of evaluation and management (3,26,31).

Table 2. Conditions Associated with Ketoacidosis and Anion Gap Metabolic Acidosis (3,23,24,26)

Type	Specific Condition	Considerations
Ketones	DKA	Serum blood glucose > 250 mg/dL and often a history of diabetes
	Starvation	History of intentional or unintentional starvation; the serum bicarbonate is usually ≥ 18 mEq/L
Uremia	Renal failure	Renal failure is present
Lactic acidosis	Sepsis, shock	A lactic acid elevation may be seen in AKA and should be directly measured; assess for signs of shock and infection
Toxins	Salicylates	Measure serum salicylate levels if the history suggests salicylate toxicity
	Toxic alcohols (e.g., ethylene glycol, methanol)	An osmolar gap should be calculated, noting AKA may have an increased osmolar gap from increased serum acetone levels; toxic alcohol toxicity should not cause ketosis

DKA = diabetic ketoacidosis; AKA = alcoholic ketoacidosis.

However, use of normal saline for resuscitation may result in hyperchloremic non-anion gap metabolic acidosis, so balanced fluids may be preferred. If hyponatremia is present, an isotonic fluid containing dextrose should be used to prevent a further decrease in the serum sodium while treating the AKA. After diagnosis of AKA and fluid resuscitation, further management is based on serum glucose and electrolyte levels.

Dextrose plays an important role in hypoglycemic or normoglycemic patients with AKA (3,4,31). It repletes serum glucose, increases insulin secretion, and decreases glucagon secretion, all of which reduce the synthesis of ketone bodies and resolve the ketoacidosis. Thus, dextrose can assist in improving the serum pH and resolving the ketoacidosis in patients with AKA (3,4,31). Patients with severe hypoglycemia (i.e., symptoms of hypoglycemia or serum glucose < 60 mg/dL) should receive dextrose 50% 50 mL (25 g) or dextrose 10% 100–250 mL. In patients without severe hypoglycemia, serum potassium should be rapidly assessed, as dextrose can increase insulin secretion and result in severe hypokalemia. In patients who are normoglycemic or mildly hypoglycemic with a potassium ≥ 3.5 mEq/L, dextrose 5% should be administered after initial fluid resuscitation (e.g., dextrose 5% with LR or normal saline [NS]) (3,31). Patients with AKA and hyperglycemia should receive an insulin infusion rather than dextrose alone to assist with resolution of the ketoacidosis (3,31).

Most patients will require electrolyte repletion (1–3,6). Patients may have hypokalemia, hypomagnesemia, and hypophosphatemia (3,18,31). If the patient demonstrates hypokalemia but normal phosphate, potassium chloride or potassium phosphate may be used. As previously discussed, serum magnesium levels are not reliable, and magnesium should be repleted with potassium. For by-mouth-tolerant patients with a serum phosphate of 1–2 mg/dL, oral potassium phosphate 250–500 mg every 12 h is recommended, but for those who are unable to tolerate oral intake, potassium phosphate 15 mmol i.v. over 2.5 h is recommended. For those with serum phosphate < 1 mg/dL, potassium phosphate 45 mmol i.v. over 7 h is recommended. Thiamine supplementation is also recommended, as thiamine forms an essential cofactor for carbohydrate metabolism and shunts pyruvate into the Krebs cycle (3,32). Those with a large carbohydrate intake (e.g., recent heavy alcohol use) more rapidly deplete thiamine reserves, and thiamine stores may already be deficient from poor nutritional intake (24,33,34). A prophylactic dose of 200 mg of thiamine intravenously is recommended along with the dextrose administration, but thiamine should not delay dextrose administration (24,34). If any of the previously discussed neurologic signs or symptoms are present, Wernicke encephalopathy should be suspected and treated. In those with AUD, the treatment dose for Wernicke encephalopathy is 500 mg i.v. thiamine three times daily (24).

It is recommended to repeat electrolyte and glucose assessment every 1–2 h to monitor for electrolyte changes and resolution of ketoacidosis, defined by serum pH > 7.35 and bicarbonate > 18 mEq/L. Sodium bicarbonate therapy is typically unnecessary, as even those with a severe acidemia (i.e., pH < 7.0) correct quickly with supportive treatment (1,3). The acidemia will not fully resolve until the beta-hydroxybutyrate levels return to normal, as the ketosis contributes to the metabolic acidosis. As discussed, intravenous fluid repletion and glucose administration will resolve the ketosis and acidosis. Renal losses of potassium, sodium hydroxybutyrate, and

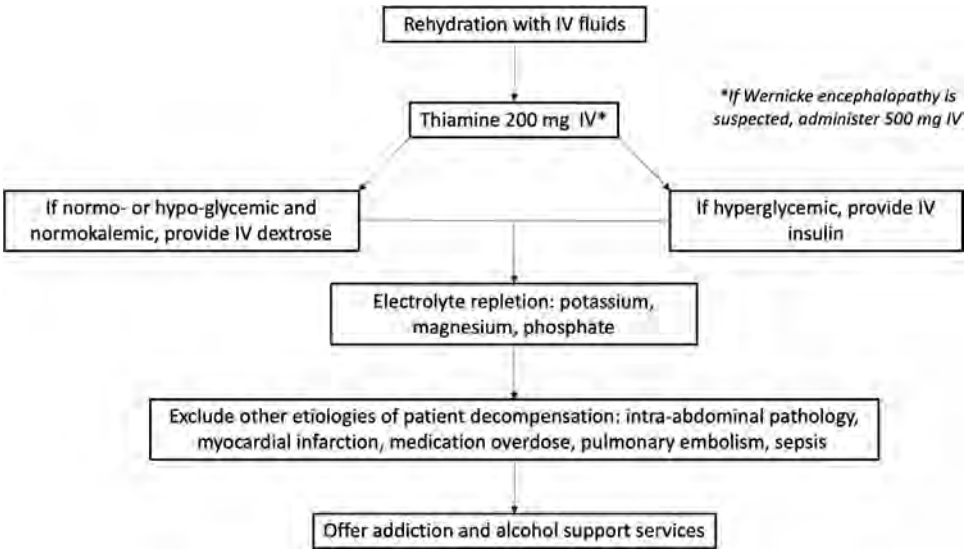

Figure 1. Alcoholic ketoacidosis management.

acetoacetate may also result in incomplete resolution of metabolic acidosis, resulting in a residual hyperchloremic metabolic acidosis. Once patients improve, clinicians should offer addiction support services (3). A case series of 74 patients demonstrated that half of cases resolve within 12 h and can be safely discharged from the ED (1). Of note, the authors of this review do not recommend observing all patients for 12 h. Patients with the ability to tolerate oral fluids, resolution of ketoacidosis and electrolyte abnormalities, and improving volume status may be discharged with follow-up. However, patients who are not able to tolerate oral fluids, have continued hemodynamic changes, or unresolved ketoacidosis should be admitted to a monitored setting (Figure 1).

Complications

Several complications may occur in the setting of delayed diagnosis and management, as well as due to patients' alcohol use. Complications associated with AKA and AUD include significant volume depletion, electrolyte abnormalities (e.g., hypokalemia, hypophosphatemia, and hypomagnesemia), and hemodynamic compromising dysrhythmias resulting in cardiac arrest. Patients with AKA may also decompensate due to untreated co-existing conditions such as hypothermia, rhabdomyolysis, pancreatitis, infection, seizure, and delirium tremens (3,35–37).

Conclusions

Alcoholic ketoacidosis occurs in patients with a history of alcohol use, poor oral intake, and ketoacidosis. Patients most commonly have a history of chronic alcohol use and often present with nausea, vomiting, and abdominal pain. However, AKA can also occur after binge drinking. Patients are dehydrated, and serum glucose can be low, normal, or mildly elevated. An anion gap metabolic acidosis with ketosis and electrolyte abnormalities are usually present on laboratory evaluation. Management includes fluid resuscitation, glucose and vitamin supplementation, electrolyte repletion, and evaluation for other conditions.

Clinical Bottom Line

The patient appears dehydrated, and 1 L of LR is administered with antiemetics. The delta-delta reveals an equal decrease in serum bicarbonate by 8 and an increase in the anion gap by 8, consistent with a pure anion gap acidosis. Further laboratory assessment reveals a beta-hydroxybutyrate level of 7.5 mmol/L. A serum alcohol level is negative, and the serum potassium is 4.2 mEq/L. The clinician suspects AKA and administers thiamine 200 mg and dextrose 10% in water. The patient is admitted to a monitored setting due to the dehydration and ketoacidosis.

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ARTICLE SUMMARY

1. Why is this topic important?

Alcoholic ketoacidosis (AKA) is a common presentation in the emergency department (ED) and requires targeted therapies.

2. What does this review attempt to show?

This review provides a summary of the background, pathophysiology, diagnosis, and management of AKA in the ED setting.

3. What are the key findings?

AKA is defined by metabolic acidosis and ketosis in a patient with alcohol use. Patients most commonly present with a history of alcohol use, decreased oral intake, gastrointestinal symptoms, and ketoacidosis. Patients are generally dehydrated, and serum glucose can be low, normal, or mildly elevated. Laboratory assessment typically reveals an anion gap metabolic acidosis with ketosis and electrolyte abnormalities. Management includes i.v. fluid resuscitation, glucose and thiamine supplementation, electrolyte repletion, and evaluation for other conditions.

4. How is patient care impacted?

By increasing awareness of this condition, clinicians can improve the care of patients with AKA.