Alcoholic Ketoacidosis

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Key Points

- Alcoholic ketoacidosis accounts for up to 20% of cases of ketoacidosis.
- The characteristic example is an alcoholic person who abruptly abstains and has signs and symptoms such as vomiting, abdominal pain, malnutrition, and an anion gap metabolic acidosis, but no measurable alcohol levels.
- Initial glucose levels may be low, normal, or high.
- A ratio of β-hydroxybutyrate to acetoacetate in excess of 10:1 is pathognomonic for alcoholic ketoacidosis, whereas a 3:1 ratio is more common in diabetic ketoacidosis.
- Treatment emphasizes hydration with dextrose-containing solutions and thiamine; resolution of the acidosis usually occurs within 6 to 12 hours.
- Mortality from uncomplicated alcoholic ketoacidosis is less than 1%.

Definition and Epidemiology

The diagnosis of alcoholic ketoacidosis (AKA) is established when an alcoholic patient is found to have an anion gap metabolic acidosis without historical or laboratory evidence suggesting an alternative cause. AKA may develop after protracted vomiting in malnourished, chronic alcoholics who consume a daily average of 200 g of ethanol. AKA generally occurs with equal frequency in adult men and women between 20 and 60 years of age. Its incidence and prevalence remain undefined. Up to one half of patients are likely to suffer recurrence. It is unclear whether these individuals have a genetic predisposition to AKA or whether they repeatedly reproduce the hormonal milieu that precipitates ketoacidosis. Almost one fifth of cases of ketoacidosis are alcoholic ketoacidosis.

Pathophysiology

The term alcoholic acidosis describes a syndrome of four types of metabolic acidosis that occur in alcoholics and vary in severity: ketoadicosis, lactic acidosis, acetic acidosis, and loss of bicarbonate in urine. AKA arises from a complicated interplay of the metabolic effects of alcohol in fasted, dehydrated alcoholics who abruptly stop their intake of ethanol. β-Hydroxybutyrate is the predominant ketoacid. Metabolism of ethanol to acetaldehyde is catalyzed by alcohol dehydrogenase in the liver and results in accumulation of the reduced form of nicotinamide adenine dinucleotide (NADH) relative to the oxidized form of nicotinamide adenine dinucleotide (NAD+). The altered ratio of NADH/NAD+ is the rate-limiting step in alcohol metabolism and favors the conversion of acetoacetate to β-hydroxybutyrate, as illustrated in Figure 161.1.

In severe cases, other mechanisms are involved as well. Impaired insulin effects, dehydration, and hormonal responses propagate the accumulation of ketoacid. Ethanol consumption, acute starvation, and catecholamine release cause a relative insulin insufficiency that acts to favor lipolysis and limit glycogen storage. The formation of ketone bodies is further promoted by a dehydration-induced stress response–related release of cortisol, growth hormone, glucagon, and catecholamines. It is unclear whether the elevated levels of cortisol and growth hormone observed in patients with AKA initiate or sustain this process. Ketone bodies in the form of ketone bodies are produced as a result of the NADH/NAD+ ratio induced by ethanol metabolism, as well as the lipolytic effect of counterregulatory hormones. Renal excretion of ketone bodies becomes impaired because of dehydration, volume contraction, and diminished renal clearance. Accumulation of ketoacid ensues.

Lactic acidosis is a common, concurrent acid-base disorder, in addition to ketoacidosis. Although lactic acidosis may result from another cause such as sepsis or seizures, alcohol consumption can cause mild accumulation of lactic acid by two distinct mechanisms. First, the elevated NADH/NAD+ ratio can shift the pyruvate–lactic acid equilibrium in favor of lactic acidosis. Second, the thiamine deficiency common in chronic alcoholics prohibits the alternative oxidation of pyruvate to acetyl coenzyme A because thiamine is a coenzyme in this reaction.

Presenting Signs and Symptoms

AKA typically develops in severe alcoholics whose recent binge drinking has abruptly and recently stopped. The sudden alcohol cessation is often due to an alcohol-related disease
such as gastritis, pancreatitis, hepatitis, or pneumonia. Concurrent starvation, abdominal pain, and protracted vomiting are common features.

Patients typically have a clear sensorium, are not confused, and are able to provide a complete history, although there are case reports of encephalopathic manifestations. Box 161.1 summarizes the sensitivity of signs and symptoms for AKA.

Tachycardia and tachypnea are typically the most remarkable findings on examination. Tachycardia results from volume depletion and early alcohol withdrawal, whereas tachypnea is generally a physiologic response to the ongoing metabolic acidosis. Hypotension and hypothermia are rare. Fever usually indicates a separate, concurrent infectious process. Abdominal examination may reveal hepatomegaly, hepatic tenderness, epigastric discomfort, or severe and diffuse tenderness. The presence of hypotension, fever, peritoneal signs, bloody stools, trauma, or altered mental status mandates a search for alternative causes of these physical findings.

**Fig. 161.1** Pathophysiology of alcoholic ketoacidosis. Alcohol dehydrogenase in hepatocyte cytosol metabolizes ethanol to acetaldehyde, which is then transported into the mitochondria for metabolism to acetate. Acetate is activated by adenosine triphosphate (ATP), coenzyme A (CoA), and acetate thiokeine to form acetyl CoA, which can (1) be oxidized to carbon dioxide (CO₂) by the citric acid cycle, (2) form ketone bodies, or (3) be converted to fat. Insulin depletion results from a number of influences, including endogenous suppression from malnutrition, the direct suppressive effects of ethanol, and α-adrenergic suppression from catecholamines. Volume depletion stimulates the counterregulatory release of catecholamines, cortisol, growth hormone, and glucagon. Glycogen depletion from malnutrition and alcoholic liver disease stimulates enhanced fatty acid release, which is further promoted by catecholamines. The relative increase in NADH over NAD⁺ resulting from the metabolism of ethanol drives several reactions to produce βOHB and lactate. Thiamine deficiency favors the conversion of pyruvate to lactate rather than acetyl CoA. ATP, Adenosine triphosphate; EtOH, ethyl alcohol; NAD⁺, oxidized form of nicotinamide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide; βOHB, β-hydroxybutyrate.
Glucose levels may be low, normal, or elevated. Diabetic alcoholics with modest elevations in glucose (>250 mg/dL) pose a particular diagnostic challenge because they may have diabetic ketoacidosis (DKA) or concurrent DKA and AKA. A useful distinguishing feature in these cases is the \( \beta \)-hydroxybutyrate–acetoacetate ratio, which is 1:1 normally, 3:1 with DKA, and 10:1 with AKA.

Because the nitroprusside reaction used in a urine dipstick tests for DKA, a negative urine dipstick test for “ketones” does not exclude AKA. In such instances, the dipstick may show paradoxical worsening of urine ketones as AKA resolves with treatment and \( \beta \)-hydroxybutyrate is converted to acetoacetate.\(^8,9\)

Hypokalemia and hypophosphatemia are common with AKA, particularly as treatment progresses. Alcohol levels are generally zero, although case reports have noted the presence of AKA even when ethanol is detectable.\(^10-12\)

**TREATMENT**

Treatment of AKA is directed at correcting three deficits: volume depletion, glycogen depletion, and the elevated NADH/NAD\(^+\) ratio. Intravenous fluid and glucose are highly effective treatments. Administration of dextrose-containing solutions to hypoglycemic or euglycemic patients stimulates NADH oxidation and replaces glycogen stores, which results in more rapid correction of acidosis than with saline alone. Antiemetics should be provided.

Initially normal levels of magnesium, potassium, and phosphorus decrease during treatment and require repletion. Intravenous thiamine supplementation (100 mg) provides theoretic prophylaxis against Wernicke encephalopathy and may help reverse the lactic acidosis. Exogenous insulin and bicarbonate therapy is rarely indicated.\(^12-14\)

**DISPOSITION**

Mortality in patients with AKA is less than 1%. Adverse outcomes are typically associated with concurrent alcohol-related complications rather than with the ketoacidosis itself. Admission for uncomplicated AKA is indicated for patients with intractable vomiting or abdominal pain of unclear cause.
If a thorough evaluation fails to reveal additional acute health issues, the acidosis can be treated and resolved within 6 to 12 hours. Discharged patients should have appropriate follow-up to address issues of chronic alcohol abuse. Patients may also benefit from an alcohol rehabilitation program (see Chapter 199). Discharge instructions should advise patients of their predisposition for recurrent episodes of AKA, as well as the potentially detrimental effect of alcohol abuse on other aspects of their health. Return precautions should include intractable vomiting, caloric starvation, and increasing abdominal pain.

REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES