Fasting ketosis and alcoholic ketoacidosis

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INTRODUCTION

Ketoacidosis is the term used for metabolic acidoses generated by an accumulation of ketone bodies. The most common cause of ketoacidosis is diabetic ketoacidosis. Two other causes are fasting ketosis and alcoholic ketoacidosis.

Fasting ketosis and alcoholic ketoacidosis will be reviewed here. Issues related to diabetic ketoacidosis are discussed in detail elsewhere.

- (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis".)
- (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis".)
- (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment".)

PHYSIOLOGY OF KETONE BODIES

There are three major ketone bodies, with the interrelationships shown in the figure (figure 1):

- Acetoacetic acid is the only true ketoacid.

- The more dominant acid in patients with ketoacidosis is beta-hydroxybutyric acid, which results from the reduction of acetoacetic acid by NADH. Beta-hydroxybutyric acid is a hydroxyacid, not a true ketoacid.

- Acetone, which is formed from the decarboxylation of acetic acid, is a true ketone but **not** an acid.

Ketone bodies are water-soluble, fat-derived fuels that are used by many tissues for energy generation when there is limited glucose availability. The brain becomes especially dependent upon ketones for fuel when plasma glucose levels are inadequate. In most patients, neurologic manifestations of hypoglycemia begin at a plasma glucose concentration of less than 50 to 55 mg/dL [2.8 to 3.0 mmol/L]. By contrast, neurologic manifestations are not typically seen until the plasma glucose concentration falls to much lower levels in patients with diabetic ketoacidosis, in part due to the availability of ketones. The shift from a metabolic state that requires glucose metabolism to one more dependent upon ketones also has other metabolic, hormonal, and signaling effects [1,2].

Hepatic generation of ketone bodies is usually stimulated by the combination of low insulin levels and high glucagon levels (ie, a low insulin/glucagon ratio) and delivery of long-chain fatty acids to the hepatic mitochondria [3-8]. Low insulin levels, which are most often secondary to absolute or relative hypoglycemia (as with fasting), activate hormone-sensitive lipase, which releases long chain fatty acids and glycerol from triglycerides in peripheral fat stores. The fatty acids are transported to the liver via the circulation where they enter hepatocyte mitochondria under the influence of low insulin and high glucagon levels.

Within the hepatocyte mitochondria, the fatty acids undergo beta-oxidation, generating acetyl-CoA. When large quantities of acetyl-CoA are generated, the oxidative capacity of the Krebs cycle may be exceeded, resulting in the entry of acetyl-CoA into the ketogenic pathway and the generation of ketone bodies. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Epidemiology and pathogenesis", section on 'Ketone production'.) [1,2]

FASTING KETOSIS

The hepatic generation of ketone bodies described in the preceding paragraph is the normal physiologic response to fasting. Mild ketosis (ketoacid concentration of approximately 1 mmol/L) generally develops after a 12- to 14-hour fast. If fasting continues, the ketoacid concentration continues to rise and peaks after 20 to 30 hours at a concentration of 8 to 10

mmol/L (mmol/L is used here rather than mEq/L since mEq/L does not apply to acetone, which has no charge). Beta-hydroxybutyrate is the major ketone body that accumulates [5-7].

At a plasma ketone body concentration of 8 to 10 mmol/L, the rate of hepatic ketone body synthesis matches the rate of ketone body utilization in the brain, muscle, kidney, and other peripheral tissues, plus a small degree of ketone body loss into the urine. The net effect is that the plasma bicarbonate concentration usually falls by 7 to 8 mEq/L (bicarbonate concentration of approximately 18 mEq/L), and the plasma anion gap is increased to a similar degree. The fall in plasma bicarbonate is often less than the rise in plasma ketone body concentration due to at least two factors: as mentioned in the preceding section, acetone is not an acid and therefore does not affect the plasma bicarbonate, and some of the hydrogen ions released from ketoacids are buffered in the cells rather than the extracellular fluid. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis", section on 'The delta AG/delta HCO3 in ketoacidosis'.)

Stabilization of ketone body generation at a moderate level is due to the following factors:

- Increased ketone body concentrations with starvation generate a "self-braking" effect on further increases in their levels. This is mediated through several factors that slow the release of fatty acids from adipose tissue: High ketone body concentrations stimulate insulin release (despite low glucose levels) [9], adipose tissue develops increased sensitivity to insulin's inhibitory effect on fatty acid release [10], and ketone bodies themselves directly inhibit lipolysis [10].

- An increased rate of central nervous system ketoacid uptake as the brain switches from glucose to ketones as its source of fuel [5,6,11].

- Increased peripheral tissue ketone utilization [12].

Since the degree of metabolic acidosis usually remains relatively mild, the term "ketosis" is typically used rather than "ketoacidosis." There is no evidence of adverse consequences associated with fasting ketosis.

In addition to fasting, limited ketosis can also be induced by a low-carbohydrate diet (carbohydrate intake usually less than 40 to 50 g/day) [13]. (See "Obesity in adults: Dietary therapy", section on 'Low-carbohydrate diets'.)

Fasting ketoacidosis — Under some conditions, fasting ketosis becomes more severe, resulting in overt ketoacidosis. The distinction between these conditions is not well defined, but we suggest that when the serum bicarbonate level falls below 18 mEq/L (and the anion gap

exceeds 18 mEq/L) as a result of an accumulation of beta-hydroxybutyric and acetoacetic acid that a state of ketoacidosis exists. This usually occurs when an individual with a large, relatively fixed metabolic requirement for glucose experiences a prolonged fast [6], as occurs with fasting in the very young (eg, normal neonates generally manifest baseline ketosis for several days) [6,7,14] or in pregnant or lactating females [6,15,16].

A number of cases of overt ketoacidosis have also been described in patients on very low-carbohydrate, high-fat diets [17,18]. The ketoacidosis in these patients is usually associated with moderate hyperglycemia.

ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis usually occurs in malnourished patients with moderate or severe alcohol use disorder who have a history of binge alcohol ingestion. Active drinking has often stopped because of the development of abdominal pain, nausea, and vomiting. After one to two days, the patient presents to the hospital. Blood ethanol concentrations at this time may be low or not detectable [19-22]. Although it had been thought that alcoholic ketoacidosis was more common in females, later studies found a similar incidence in males and females [19,23-25].

Pathophysiology — Ethanol is rapidly oxidized, mainly by hepatocytes, first to acetaldehyde and then to acetic acid. The acetic acid may be exported from the liver to be utilized for energy or converted to acetyl-CoA [19,26]. The acetyl-CoA can enter one of three possible pathways: oxidation in the Krebs cycle; fatty acid synthesis; or ketogenesis forming acetoacetic acid, beta-hydroxybutyric acid, and acetone. (See 'Physiology of ketone bodies' above.)

As noted above, liberal peripheral release of fatty acids and their delivery to the liver is required for the development of brisk ketogenesis. A low insulin/glucagon ratio is a prerequisite for major hepatic fatty acid oxidation. Although mild to moderate ketoacidosis can develop during active alcohol ingestion, severe ketoacidosis usually only occurs after ethanol ingestion has ceased. During active ethanol ingestion, its metabolism generates acetate and acetyl-CoA, which inhibit peripheral lipolysis, and this limits fatty acid delivery to the liver [19,26].

However, once ethanol concentrations begin to fall, increased levels of catecholamines (particularly norepinephrine) and cortisol resulting from ethanol withdrawal amplify the hormonal responses to fasting (low insulin levels, high glucagon), causing a marked increase in lipolysis [27-29]. The oxidation of ethanol to acetaldehyde and then to acetic acid each converts NAD+ to NADH [30]. This redox shift of the NAD+/NADH ratio toward NADH has the following effects:

- It suppresses gluconeogenesis and may result in hypoglycemia [31,32].

- It drives the acetoacetic acid/beta-hydroxybutyric acid ratio toward beta-hydroxybutyric acid (figure 1) [31,32]. The shift from acetoacetic acid to beta-hydroxybutyric acid has no effect on the degree of bicarbonate reduction or anion gap elevation, since both acids have an identical effect on these parameters. However, the redox shift may have diagnostic implications when the nitroprusside test is used, since this test detects acetoacetate and, to a much lesser degree, acetone but does not react with beta-hydroxybutyrate, which accounts for the majority of ketoacids. (See 'Detection of ketone bodies' below and 'False-negative nitroprusside testing' below.)

- It favors the conversion of pyruvate to lactate. This effect is usually not important clinically, and a significant lactic acidosis in a patient with alcoholic ketoacidosis should prompt a search for other, more common disorders that are causes of a marked reduction in tissue perfusion, such as hypovolemia, heart failure, or sepsis. (See 'Combined acid-base disorders' below and "Causes of lactic acidosis", section on 'Pathophysiology'.)

Clinical presentation — Patients with alcoholic ketoacidosis typically present with a history of chronic unhealthy alcohol use, malnutrition, and a recent episode of binge drinking [19-25,29,30]. There is often a history of recurrent episodes.

A variety of clinical manifestations are commonly seen in patients with alcoholic ketoacidosis [19-25,29,30]. They include:

- Nausea, vomiting, and abdominal pain which, in a series of 74 patients, were present in 76, 73, and 62 percent of patients, respectively [19]. These symptoms typically develop at the end of the binge, as described in the preceding section (see 'Pathophysiology' above), and may persist for one to two days **prior** to presentation with ketoacidosis. They may be due to the acute effects of ethanol, such as esophagitis, gastritis, hepatitis, or pancreatitis, or to an unrelated medical condition.

- Generalized abdominal tenderness, hepatomegaly, and laboratory evidence of alcoholic hepatitis (high serum transaminase and bilirubin) and/or pancreatitis (high serum amylase and lipase).

- Hypovolemia and/or potassium depletion, which can result from gastrointestinal losses, as with vomiting or diarrhea, urinary losses driven by renal excretion of sodium and potassium with ketoacid anions (mostly beta-hydroxybutyrate), and third-spacing if pancreatitis develops. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'.)

- Tachycardia and hypertension due to alcohol withdrawal, pancreatitis, and/or volume depletion, as outlined above.

- Increased respiratory rate, due to alcohol withdrawal, pain, chronic liver disease, and/or respiratory compensation for the metabolic acidosis. (See "Simple and mixed acid-base disorders", section on 'Compensatory respiratory and renal responses'.)

In contrast to patients with diabetic ketoacidosis, patients with alcoholic ketoacidosis are usually **alert and lucid** despite severe ketoacidosis [19,24,25,33]. The exception is patients with delirium caused by ethanol withdrawal.

A probable explanation for this difference is that the neurologic manifestations of diabetic ketoacidosis, which are even more common in patients with nonketotic hyperosmolar hyperglycemia, are primarily due to a marked rise in the effective plasma osmolality (ie, not including urea, which is an ineffective osmole since it equilibrates across cell membranes). Water loss induced by the osmotic diuresis is a major contributor to the rise in effective plasma osmolality. These factors are **not** present in alcoholic ketoacidosis.

Laboratory findings — For the reasons described above, plasma alcohol concentrations may be low or **not** detectable at presentation in patients with alcoholic ketoacidosis, since clinically significant ketone body formation typically occurs as ethanol concentrations fall [19,34]. (See 'Pathophysiology' above.)

The detection of ketone bodies in such patients is discussed below. Several changes in laboratory methodology have had a major impact on these measurements. (See 'Detection of ketone bodies' below.)

Patients with alcoholic ketoacidosis may have a variety of other laboratory abnormalities, as described in the following sections.

Hypoglycemia or hyperglycemia — Plasma glucose concentrations may be reduced, normal, or modestly elevated but are almost always less than 275 mg/dL (15.3 mmol/L) [19,24]. In a series of 74 patients with alcoholic ketoacidosis, nine (12 percent) had a plasma glucose less than 60 mg/dL (3.3 mmol/L), and eight (11 percent) had a plasma glucose greater than 250 mg/dL (13.9 mmol/L) [19]. None of the patients had a history of diabetes mellitus or subsequent evidence of glucose intolerance after initial treatment in the hospital. However, some patients with alcoholic ketoacidosis will undoubtedly also have concurrent diabetes mellitus. Measurement of hemoglobin A1C may be helpful since an elevated value suggests chronic hyperglycemia.

Potassium depletion and hypokalemia — Potassium deficits can be induced by both gastrointestinal losses (vomiting or diarrhea) and/or urinary losses caused by the excretion of potassium salts of ketone anions (beta-hydroxybutyrate and, to a lesser degree, acetoacetate) (see "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'). Poor nutrition and reduced oral potassium intake also contribute to potassium deficits and hypokalemia in patients with alcoholic ketoacidosis.

There are additional issues related to potassium balance in patients with alcoholic ketoacidosis. In some forms of metabolic acidosis, potassium moves from cells into the extracellular fluid and raises the plasma potassium concentration. This occurs because more than one-half of the excess hydrogen ions are buffered in the cells, with electroneutrality being maintained by potassium movement from the cells into the extracellular fluid (figure 2). By contrast, potassium shift out of the cells is much **less likely** to occur in ketoacidosis due, at least in part, to the ability of the hydrogen ion and the ketoacid anion to enter the cells together via a sodium-organic anion cotransporter [35]. A similar process occurs in lactic acidosis (figure 3). (See "Potassium balance in acid-base disorders", section on 'Metabolic acidosis' and "Causes and evaluation of hyperkalemia in adults", section on 'Absent effect in lactic acidosis or ketoacidosis'.)

Unlike diabetic ketoacidosis, alcoholic ketoacidosis does not generate substantial potassium redistribution from cells into the extracellular space. Potassium redistribution in diabetic ketoacidosis is largely due to factors other than acidosis, including hyperosmolality (caused by hyperglycemia) and insulin deficiency. These factors are absent in patients with alcoholic ketoacidosis who typically have normal, or minimally elevated, blood glucose. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum potassium'.)

Phosphate depletion and hypophosphatemia — Phosphate depletion is common in patients with alcohol use disorder who often have decreased phosphate intake, reduced intestinal phosphate absorption, and/or increased urinary phosphate excretion. (See "Hypophosphatemia: Evaluation and treatment", section on 'Patients with alcohol use disorder'.)

Despite the phosphate depletion, the plasma phosphate concentration may initially be normal or elevated because both metabolic acidosis and low insulin levels promote phosphate movement out of the cells. The transcellular phosphate shift is reversed, and overt hypophosphatemia often occurs early in the hospitalization. One or both of the following factors are primarily responsible for the movement of phosphate into the cells after

hospitalization: dextrose administration, which stimulates the release of insulin; and alcohol withdrawal, which may be associated with acute respiratory alkalosis. (See "Hypophosphatemia: Evaluation and treatment", section on 'Patients with alcohol use disorder' and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum phosphate'.)

Magnesium depletion and hypomagnesemia — Magnesium depletion is common in patients with alcoholic ketoacidosis. In the study of 74 patients with alcoholic ketoacidosis cited above, hypomagnesemia was present in approximately 20 percent [19]. A variety of factors may contribute including dietary deficiency, urinary magnesium wasting, diarrhea, and acute pancreatitis. Renal magnesium wasting may be a result of chronic alcohol ingestion and also is exacerbated by metabolic acidosis [36]. (See "Hypomagnesemia: Causes of hypomagnesemia", section on 'Alcohol'.)

Elevated serum osmolal gap — The serum osmolal gap represents the difference between the measured serum osmolality and the calculated value derived from the concentrations of sodium, glucose, blood urea nitrogen, and ethanol. Calculators using standard international (SI) units and conventional units are provided (calculator 1 and calculator 2). (See "Serum osmolal gap".)

Patients with alcoholic ketoacidosis can have an elevated serum osmolal gap. The magnitude of the elevation was evaluated in a study of 19 patients with alcoholic ketoacidosis and 10 randomly selected controls [34]. The serum osmolal gap, using a calculated osmolality that did not account for ethanol, was significantly higher in the patients with alcoholic ketoacidosis (mean 27 versus 2 mosmol/kg). At least two factors contributed to the increase in serum osmolal gap: elevated serum ethanol concentrations at presentation and elevated serum acetone concentrations, which may persist for some period after the ethanol has been metabolized [34]. The ketone body anions, mostly beta-hydroxybutyrate, do not contribute to the serum osmolal gap, since the anions have accompanying cations (mostly sodium) and are therefore accounted for in the two-times-the-serum-sodium term in the formula for the serum osmolal gap (calculator 1 and calculator 2).

Combined acid-base disorders — Alcoholic ketoacidosis is often associated with other acid-base disorders [19,26,30]. The frequency with which combined acid-base disorders occurs was illustrated in the study of 74 patients with alcoholic ketoacidosis cited above [19].

Among the 40 patients in whom arterial blood gas measurements were obtained, nine (23 percent) had a simple increased anion gap metabolic acidosis (with appropriate respiratory compensation). The remaining patients had a variety of mixed acid-base disorders:

- Ten (25 percent) had a mixed anion gap metabolic acidosis plus a respiratory alkalosis. Chronic respiratory alkalosis may be present in patients with underlying hepatic disease, and acute respiratory alkalosis can be induced by the stress of ethanol withdrawal. (See "Simple and mixed acid-base disorders", section on 'Compensatory respiratory and renal responses'.)

- Eleven (28 percent) had a mixed anion gap metabolic acidosis plus a metabolic alkalosis (usually caused by vomiting). The net effect was that the fall in plasma bicarbonate concentration was less than the increase anion gap. In some patients, the two disorders were of comparable severity, and the arterial pH was normal or near normal. In this setting, an increased anion gap and ketonuria are the primary signs of underlying ketoacidosis. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

- Six (15 percent) had a mixed anion gap metabolic acidosis plus a hyperchloremic metabolic acidosis. In these patients, the fall in plasma bicarbonate was significantly greater than the increase in anion gap, and they therefore had a component of hyperchloremia. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis".)

  There are at least two possible mechanisms for a combined high anion gap and normal anion gap (hyperchloremic) metabolic acidosis in patients with alcoholic ketoacidosis:

  - The most common cause is the loss of ketoacid anions (beta-hydroxybutyrate and acetoacetate) into the urine with sodium or potassium. Such urinary loss of sodium or potassium ketoanion salts represents the loss of "potential bicarbonate" and will lower the plasma anion gap toward normal but not raise the serum bicarbonate. By contrast, the loss of ketoacid anions with either hydrogen or ammonium will lower the anion gap and raise the serum bicarbonate concentration toward normal.

  - Another cause of hyperchloremic metabolic acidosis may be present, such as diarrhea or renal tubular acidosis. (See "The delta anion gap/delta HCO3 ratio in patients with a high anion gap metabolic acidosis", section on 'The delta AG/delta HCO3 in ketoacidosis'.)

- Some patients had a combined high anion gap acidosis due to both ketoacidosis and lactic acidosis. Among the 38 patients in whom serum lactate concentrations were measured, 23 (61 percent) had an elevated value, but only five patients (13 percent) had values above 6 mEq/L (maximum 9 mEq/L). All of these patients had a serious concurrent disease that

could have contributed to or been solely responsible for the lactic acidosis, such as sepsis, pancreatitis, and rhabdomyolysis.

DIAGNOSIS

The diagnosis of ketosis or ketoacidosis is suggested by an elevated anion gap and confirmed by detecting the presence of ketone bodies. The distinction of fasting ketosis from alcoholic ketoacidosis and of both of these disorders from diabetic ketoacidosis is a clinical judgment based upon the history, the severity of the disorder, and the serum glucose concentration (see "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Alcoholic and fasting ketoacidosis'):

- Although ketoacidosis with a normal serum glucose may be diagnostic of alcoholic ketoacidosis, diabetic ketoacidosis can also present with a normal or relatively low blood glucose concentration. "Euglycemic" diabetic ketoacidosis can complicate diabetes in the very young and in pregnant females and is also increasingly recognized in patients with diabetes who are treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors [37]. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum glucose'.)

- Ketoacidosis with hyperglycemia is suggestive of diabetic ketoacidosis, but modest elevations in serum glucose can occur in alcoholic ketoacidosis. In a study cited above of 74 patients with alcoholic ketoacidosis, 11 percent had a serum glucose concentration greater than 250 mg/dL (13.9 mmol/L) [19]. None of these patients had a history of diabetes mellitus or subsequent evidence of glucose intolerance after initial treatment in the hospital. Measurement of hemoglobin A1C may be helpful in this setting since an elevated value suggests chronic hyperglycemia.

- Fasting ketosis rarely reduces the bicarbonate level below 17 to 18 mEq/L. (See 'Fasting ketoacidosis' above.)

Detection of ketone bodies — Confirmation of the diagnosis of ketosis or ketoacidosis requires the demonstration of ketone bodies in the urine (ketonuria) and serum (ketonemia). The presence of ketone bodies can be detected by nitroprusside testing and by direct assays of beta-hydroxybutyrate concentrations in serum. These issues are discussed in detail elsewhere, but this section will provide a brief review.

Nitroprusside testing — Urine dipstick testing with nitroprusside tablets or reagent sticks has the advantage of the results being available within minutes. Serum ketone testing is necessary

to determine whether serum ketone concentrations can explain the high anion gap acidosis. A 4+ reaction with serum diluted 1:1 is highly suggestive of ketoacidosis. A 4+ reaction in more dilute serum (ie, 1:4, 1:8, etc) provides evidence of even higher concentrations of acetoacetic acid. Although one cannot directly extrapolate from the nitroprusside result to the severity of the acidosis or the magnitude of the anion gap, this semiquantitative test is helpful in evaluating ketoacidosis as a diagnostic possibility.

Although the nitroprusside reaction is widely used to detect ketone bodies, the clinician must be aware of both **false-negative** results and, in selected settings, **false-positive** results.

False-negative nitroprusside testing — Nitroprusside reacts with acetoacetate and, to a much lesser degree, acetone (which is not an acid). However, nitroprusside does **not** react with beta-hydroxybutyrate. This is an important limitation since beta-hydroxybutyrate is usually present at higher concentrations than acetoacetate. The ratio of beta-hydroxybutyrate to acetoacetate is normally 1:1, increases to 3:1 in diabetic ketoacidosis, and may increase to 10:1 in alcoholic ketoacidosis [29]. The higher beta-hydroxybutyrate-to-acetoacetate ratio in patients with alcohol use disorder is due to a lower NAD+/NADH ratio generated by alcohol metabolism. Thus, in most patients with alcoholic ketoacidosis, nitroprusside tests initially **underestimate** the degree of ketone bodies in plasma, and some patients may have falsely negative tests [9,11].

False-positive nitroprusside testing — Drugs that contain free sulfhydryl groups, such as captopril, penicillamine, and mesna, can interact with the nitroprusside reagent and generate a false-positive nitroprusside test.

Direct measurement of serum beta-hydroxybutyrate — Because of the potential limitations described in the preceding section, the nitroprusside test is being replaced by direct assays of beta-hydroxybutyrate concentrations in serum. Several beta-hydroxybutyrate assay instruments are commercially available [29,38]. Use of such instruments will eliminate the problems associated with nitroprusside testing. One limitation is that most of these assays cannot be quantitated above a level of 6 mEq/L. In addition, an ideal assay would measure the concentration of acetoacetate as well as beta-hydroxybutyrate.

Differential diagnosis — When a patient with a history of alcohol use disorder presents with a high anion gap metabolic acidosis, alcoholic ketoacidosis must be distinguished from other causes, including diabetic ketoacidosis, lactic acidosis, and poisoning due to methanol or ethylene glycol. Patients with alcohol use disorder may also develop chronic kidney disease and uremic acidosis (table 1). (See "Approach to the adult with metabolic acidosis".)

The cause of the high anion gap metabolic acidosis is often suspected from the history and physical examination, and then confirmed with laboratory testing. The following tests should be performed:

- Urine and serum ketone bodies (using nitroprusside tests and/or beta-hydroxybutyrate measurement). (See 'Detection of ketone bodies' above.)

- Serum glucose concentrations can help distinguish diabetic ketoacidosis from alcoholic ketoacidosis. Alcoholic ketoacidosis rarely presents with glucose concentrations above 275 mg/dL (15.3 mmol/L) and are often normal or even reduced. Glucose levels are usually much higher with diabetic ketoacidosis. However, relatively low or normal glucose levels can occasionally occur with diabetic ketoacidosis ("euglycemic diabetic ketoacidosis"). This is more common in pregnant patients and in patients with diabetes who are treated with SGLT2 inhibitors. (See 'Hypoglycemia or hyperglycemia' above and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum glucose'.)

- Serum creatinine to detect advanced kidney disease. (See "Pathogenesis, consequences, and treatment of metabolic acidosis in chronic kidney disease".)

- Serum lactate to detect lactic acidosis, which is most often seen in patients with marked hypoperfusion due to hypovolemia, sepsis, or advanced heart failure. (See "Causes of lactic acidosis".)

- Serum salicylates (aspirin) when excessive use or overdose is suspected. A serum salicylate concentration should also be ordered when the serum anion gap is low or negative. (See "Salicylate (aspirin) poisoning: Clinical manifestations and evaluation".)

- Serum osmolality (measured with a freezing point depression osmometer) compared with simultaneous calculated serum osmolality to determine the osmolal gap (if ethanol is present in the blood, its osmotic contribution must be considered); if suspected, measurement of toxic alcohol (methanol or ethylene glycol) concentrations. (See "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis", section on 'Laboratory evaluation' and "Methanol and ethylene glycol poisoning: Pharmacology, clinical manifestations, and diagnosis", section on 'Urine testing'.)

  In addition to patients with ethylene glycol or methanol poisoning, an elevated serum osmolal gap can be seen in patients with alcoholic ketoacidosis, which results from high ethanol concentrations early and high acetone levels late after ethanol has been

metabolized (see 'Elevated serum osmolal gap' above). Isopropyl alcohol, which is metabolized to acetone, may also produce a large osmolal gap due to the elevation of both isopropyl alcohol and acetone levels, although it does not lead to metabolic acidosis. Serum and urine ketone tests that detect acetone (nitroprusside-based tests) will also become positive. (See "Serum osmolal gap" and "Isopropyl alcohol poisoning", section on 'Laboratory evaluation'.)

TREATMENT

The acidemia in all forms of ketoacidosis corrects at least partially with appropriate treatment of the underlying disease, which slows the rate of ketogenesis and allows peripheral tissues and the brain to metabolize the ketone bodies. Oxidation of beta-hydroxybutyrate and acetoacetate (but not acetone) results in the regeneration of bicarbonate.

Correction of the acidemia is usually **not complete** after restoration of normal beta-hydroxybutyrate and acetoacetate concentrations. The reason for incomplete resolution of the metabolic acidosis is the antecedent renal loss of sodium and potassium hydroxybutyrate and acetoacetate. The loss of these organic acid salts represents lost "potential bicarbonate." During this later phase of recovery, the patient will manifest a hyperchloremic metabolic acidosis. If kidney function is adequate, the kidneys will regenerate bicarbonate by excreting ammonium chloride and thereby restore normal acid-base and electrolyte balance.

Thiamine and dextrose in patients with alcohol use disorder — In patients with alcohol use disorder, 500 mg of thiamine should be given intravenously. It has been suggested that thiamine be given **prior** to any glucose-containing solutions to decrease the risk of precipitating or, if present, exacerbating Wernicke's encephalopathy [39-41]. However, the evidence supporting the necessity of prior thiamine therapy is weak and is limited to isolated case reports [42,43]. In patients with hypoglycemia, glucose administration should **not** be delayed pending administration of thiamine, which should be given as soon as possible. (See "Management of moderate and severe alcohol withdrawal syndromes", section on 'Symptom control and supportive care'.)

Dextrose and saline solutions — In patients with alcoholic or fasting ketoacidosis, at least partial correction of the metabolic acidosis can usually be achieved by the administration of dextrose and saline solutions [6,7,19,20,24,25,30,33,44]. These benefits are mediated by the following mechanisms:

- Dextrose administration will increase insulin secretion and reduce glucagon secretion. The resulting increase in the insulin/glucagon ratio slows hepatic fatty acid oxidation and ketoacid generation. Higher insulin concentrations also inhibit hormone-sensitive lipase in adipose tissue, which reduces fatty acid release from peripheral fat. Both effects slow ketone body synthesis. Simultaneously, metabolism of beta-hydroxybutyrate and acetoacetate, largely in the brain and muscle regenerates bicarbonate and **partially** corrects the metabolic acidosis. The mechanism of partial correction is described above (see 'Treatment' above).

- Saline (or a near isotonic balanced electrolyte solution) will replete extracellular fluid deficits, which are most often due to vomiting (present in 73 percent of patients in a series of 74 patients cited above) [19] and the loss of sodium (and potassium) in the urine with beta-hydroxybutyrate and acetoacetate anions to maintain electroneutrality. In addition, extracellular volume repletion will reduce the secretion of hormones stimulated by hypovolemia, such as catecholamines and glucagon, that promote ketogenesis [45].

The rates of dextrose and saline infusion must be adjusted on the basis of each patient's clinical and biochemical findings. In addition, the clinician must be aware of settings in which initial therapy with saline alone is preferred due to potential adverse effects of dextrose:

- As noted above, some patients with alcoholic ketoacidosis present with overt hyperglycemia. Such patients may require insulin administration rather than intravenous dextrose. (See 'Hypoglycemia or hyperglycemia' above.)

- Dextrose solutions should also be initially avoided in patients with severe hypokalemia since it stimulates insulin secretion, which drives potassium into the cells and can worsen the hypokalemia. (See 'Potassium depletion and hypokalemia' above.)

Potassium administration — Potassium depletion in patients with alcoholic ketoacidosis can result from vomiting and from urinary losses as potassium (and sodium) are excreted with ketone body anions to maintain electroneutrality. In addition, dextrose infusion stimulates insulin secretion, which drives potassium into cells and can worsen the hypokalemia. (See 'Clinical presentation' above and 'Potassium depletion and hypokalemia' above.)

Hypokalemia due to potassium depletion is corrected with oral and/or intravenous replacement. The rate of potassium administration will depend upon the severity of hypokalemia. Treatment regimens are discussed elsewhere. (See "Clinical manifestations and treatment of hypokalemia in adults", section on 'Treatment'.)

Phosphate administration — Phosphate depletion is common in individuals with alcohol use disorder. However, the serum phosphate concentration may be normal or elevated at presentation since both metabolic acidosis and insulin deficiency promote phosphate movement out of the cells. The transcellular shift is reversed, and the true state of phosphate depletion is unmasked with dextrose administration. (See 'Phosphate depletion and hypophosphatemia' above.)

Phosphate therapy in alcoholic ketoacidosis and other forms of ketoacidosis are discussed elsewhere. (See "Hypophosphatemia: Evaluation and treatment", section on 'Patients with alcohol use disorder' and "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Treatment", section on 'Phosphate depletion'.)

Magnesium administration — Hypomagnesemia is a relatively common problem in alcoholic ketoacidosis, occurring in approximately 20 percent of patients in one study [19]. (See 'Magnesium depletion and hypomagnesemia' above.)

Oral magnesium replacement may be difficult because magnesium salts are poorly absorbed and can produce diarrhea. Thus, parenteral magnesium administration is often required in patients with severe depletion. In addition, some patients have clinically significant magnesium depletion with refractory hypokalemia and hypocalcemia despite normal serum magnesium concentrations. (See "Hypomagnesemia: Evaluation and treatment".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fluid and electrolyte disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- Ketoacidosis is the term used for metabolic acidoses associated with an accumulation of ketone bodies. The most common cause of ketoacidosis is diabetic ketoacidosis. Two other causes are fasting ketosis and alcoholic ketoacidosis. (See 'Introduction' above.)
- There are three major ketone bodies, with the interrelationships shown in the figure (figure 1) (see 'Physiology of ketone bodies' above):
  - Acetoacetic acid is the only true ketoacid.

- The more dominant acid in patients with ketoacidosis is beta-hydroxybutyric acid, which results from the reduction of acetoacetic acid by NADH. Beta-hydroxybutyric acid is a hydroxyacid, not a true ketoacid.

- Acetone, which is formed from the decarboxylation of acetic acid, is a true ketone but **not** an acid.

- Hepatic generation of ketone bodies is usually stimulated by the combination of low insulin levels and high glucagon levels (ie, a low insulin/glucagon ratio that can result, for example, from fasting). (See 'Physiology of ketone bodies' above.)

- Mild ketosis generally develops after a 12- to 14-hour fast. As fasting continues, the plasma ketone body concentration usually stabilizes at 8 to 10 mmol/L. Beta-hydroxybutyrate is the major ketone body that accumulates. (See 'Fasting ketosis' above.)

- In normal fasting subjects, when the plasma ketone body concentration is 8 to 10 mmol/L, the rate of hepatic ketone body synthesis matches the rate of ketone body utilization in the brain, muscle, kidney, and other peripheral tissues, plus a small degree of ketone body loss into the urine. The net effect is that the plasma bicarbonate concentration usually falls by 7 to 8 mEq/L (bicarbonate concentration of approximately 18 mEq/L), and the plasma anion gap is increased to a similar degree. Since the degree of ketoacidosis usually remains relatively mild, the term "ketosis" is typically used rather than "ketoacidosis." There is no evidence of adverse effects associated with fasting ketosis, unless there is a relatively large glucose requirement, as occurs with fasting in the very young or in pregnant or lactating women. (See 'Fasting ketosis' above.)

- Alcoholic ketoacidosis usually occurs in malnourished patients with chronic alcohol use disorder who have a history of binge alcohol ingestion. Active drinking has often stopped because of the development of abdominal pain, nausea, and vomiting. Blood ethanol concentrations at this time may be low or not detectable. (See 'Alcoholic ketoacidosis' above.)

- As ethanol concentrations begin to fall, increased levels of catecholamines (particularly norepinephrine) and cortisol resulting from ethanol withdrawal amplify the hormonal responses to fasting (low insulin levels, high glucagon), causing a marked increase in lipolysis and fatty acid delivery to the liver. (See 'Pathophysiology' above.)

- Patients with alcoholic ketoacidosis typically present with a history of chronic alcohol use disorder, malnutrition, and a recent episode of binge drinking. A variety of clinical

manifestations are commonly seen in patients with alcoholic ketoacidosis, including (see 'Clinical presentation' above):

  - Nausea, vomiting, and abdominal pain
  - Generalized abdominal tenderness, hepatomegaly, and laboratory evidence of alcoholic hepatitis and/or pancreatitis
  - Hypovolemia and/or potassium depletion
  - Tachycardia and hypertension due to alcohol withdrawal, pancreatitis, and/or volume depletion, as outlined above
  - Increased respiratory rate, due to alcohol withdrawal, pain, and/or respiratory compensation for the metabolic acidosis

- Plasma alcohol concentrations may be low or undetectable at presentation in patients with alcoholic ketoacidosis. In addition, such patients may have hypoglycemia or hyperglycemia, hypokalemia, hypophosphatemia, hypomagnesemia, an elevated serum osmolal gap, and mixed acid-base disorders. (See 'Laboratory findings' above.)

- The diagnosis of ketosis or ketoacidosis is suggested by an elevated anion gap and confirmed by detecting the presence of ketone bodies. The distinction of fasting ketosis from alcoholic ketoacidosis and of both of these disorders from diabetic ketoacidosis is a clinical judgment based upon the history, whether the patient has ketoacidosis or ketosis (as defined above), and the serum glucose concentration. (See 'Diagnosis' above.)

- Confirmation of the diagnosis of ketosis or ketoacidosis requires the demonstration of ketone bodies in the urine (ketonuria) and serum (ketonemia). The presence of ketone bodies can be detected by nitroprusside testing (although this will be low in patients with alcoholic ketoacidosis) and by direct assays of beta-hydroxybutyrate levels in serum. (See 'Detection of ketone bodies' above.)

- When a patient with a history of alcohol use disorder presents with a high anion gap metabolic acidosis, alcoholic ketoacidosis must be distinguished from other causes, including diabetic ketoacidosis, lactic acidosis, poisoning due to methanol or ethylene glycol, and, in patients with advanced, usually chronic kidney disease, uremic acidosis (table 1). (See 'Differential diagnosis' above.)

- The acidemia in all forms of ketoacidosis corrects at least partially with appropriate treatment of the underlying disease, which slows the rate of ketogenesis. As peripheral

tissues and the brain continue to metabolize the ketone bodies, their levels will progressively fall. Oxidation of beta-hydroxybutyrate and acetoacetate (but not acetone) results in the regeneration of bicarbonate. Correction of the acidemia is usually **not complete** with treatment of the underlying disease since the urinary loss of beta-hydroxybutyrate and acetoacetate with sodium or potassium to maintain electroneutrality represents the loss of "potential bicarbonate." (See 'Treatment' above.)

- In patients with alcohol use disorder, 500 mg of thiamine should be given intravenously. When hypoglycemia is present in patients with known or suspected thiamine deficiency, we recommend that dextrose be administered immediately and **not** be withheld pending administration of thiamine. Concerns that the administration of glucose before thiamine will precipitate or exacerbate Wernicke's encephalopathy are not supported by the medical literature. Thiamine should, however, be given as soon as possible after dextrose administration. (See 'Thiamine and dextrose in patients with alcohol use disorder' above.)

- In patients with alcoholic or fasting ketoacidosis, at least partial correction of the ketoacidosis can usually be achieved by the administration of dextrose and saline solutions. However, some patients with alcoholic ketoacidosis present with overt hyperglycemia. Such patients may require insulin administration rather than intravenous dextrose. Dextrose solutions should also be avoided in patients with severe hypokalemia since it stimulates insulin secretion, which drives potassium into the cells and can worsen the hypokalemia. (See 'Dextrose and saline solutions' above.)

- Patients with alcoholic ketoacidosis may also require administration of potassium, phosphate, and magnesium. (See 'Potassium administration' above and 'Phosphate administration' above and 'Magnesium administration' above.)

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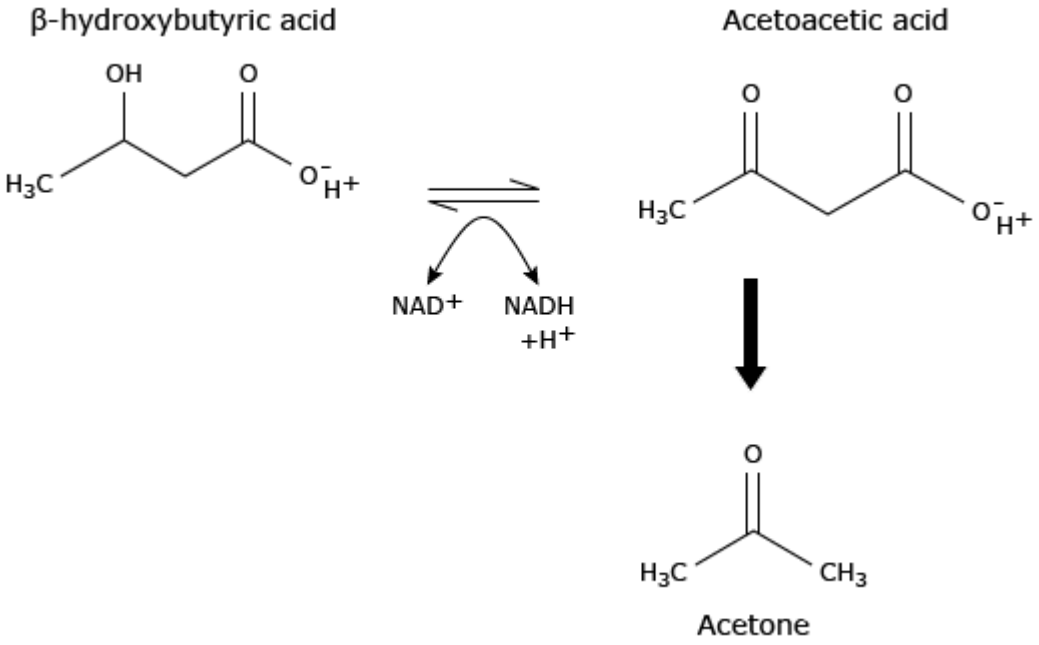
Topic 2337 Version 25.0

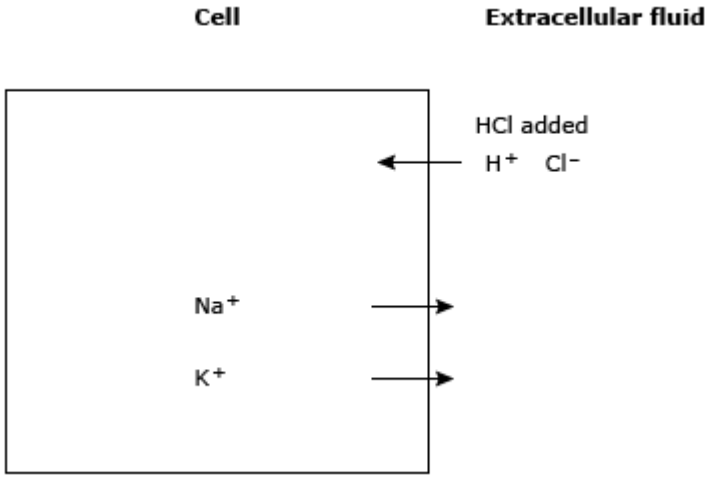
GRAPHICS

Ketone bodies



Graphic 87660 Version 1.0

Ion redistribution after acid load

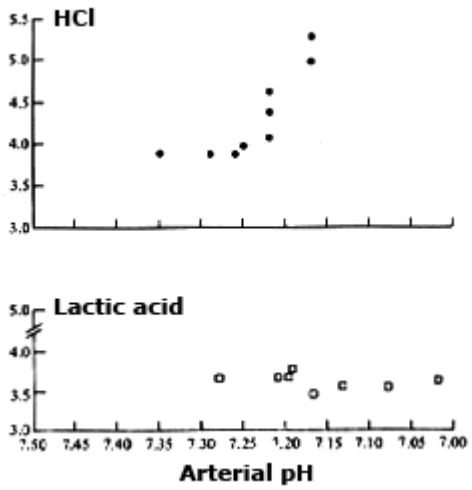


Effect of an HCl load on the distribution of Cl^-, Na^+, and K^+. As H^+ enters the cells to be buffered, intracellular Na^+ and K^+ leave the cells and move into the extracellular fluid, tending to raise the plasma K^+ concentration. These ion shifts are reversed when H^+ are removed from the extracellular fluid.

HCl: hydrogen chloride; H^+: hydrogen; Cl^-: chloride; Na^+: sodium; K^+: potassium.

Graphic 68866 Version 4.0

Acidemia and the plasma potassium



Change in the plasma K+ concentration in relation to the arterial pH in experimentally induced hydrochloric acidosis (HCl is a mineral acid) and lactic acidosis in dogs. Only HCl induced hyperkalemia.

Data from: Perez GO, Oster JR, Vaamonde CA. Serum potassium concentration in acidemic states. Nephron 1981; 27:233.

Graphic 57068 Version 7.0

Major causes of metabolic acidosis

Mechanism of acidosis	Increased AG	Normal AG
Increased acid production	Lactic acidosis	
	Ketoacidosis	
	Diabetes mellitus	
	Starvation	
	Alcohol associated	
	Ingestions	
	Methanol	
	Ethylene glycol	
	Salicylates	
	Toluene (if early or if kidney function is impaired)	Toluene ingestion (if late and if kidney function is preserved; due to excretion of sodium and potassium hippurate in the urine
	Diethylene glycol	
	Propylene glycol	
	D-lactic acidosis	A component of non-AG metabolic acidosis may coexist due to urinary excretion of D-lactate as Na and K salts (which represents potential HCO_3)
	Pyroglutamic acid (5-oxoproline)	
Loss of bicarbonate or bicarbonate precursors		Diarrhea or other intestinal losses (eg, tube drainage)
		Type 2 (proximal) RTA
		Posttreatment of ketoacidosis
		Carbonic anhydrase inhibitors
		Ureteral diversion (eg, ileal loop)
Decreased renal acid excretion	Severe kidney dysfunction (eGFR <15 to 20 mL/min/1.73 m^2)	Moderate kidney dysfunction (eGFR >15 to 20 mL/min/1.73 m^2
		Type 1 (distal) RTA (hypokalemic)
		Hyperkalemic RTA

		Type 4 RTA (hypoaldosteronism)
		Voltage defect
Large volume infusion of normal saline		Diffusion acidosis

AG: anion gap; RTA: renal tubular acidosis.

Graphic 77464 Version 15.0