TABLE 27-3 CAUSES OF LACTIC ACIDOSIS

I. Type A (tissue underperfusion and/or hypoxia)
  A. Cardiogenic shock
  B. Septic shock
  C. Hemorrhagic shock
  D. Acute hypoxia
  E. Carbon monoxide poisoning
  F. Anemia
II. Type B (absence of hypotension and hypoxia)
  A. Hereditary enzyme deficiency (glucose-6-phosphatase)
  B. Drugs or toxins
    1. Phenformin, metformin
    2. Cyanide
    3. Salicylate, ethylene glycol, methanol
    4. Propylene glycol
    5. Linezolid
    6. Propofol
    7. Nucleoside reverse transcriptase inhibitors (stavudine, didanosine)
  C. Systemic disease
    1. Liver failure
    2. Malignancy

substrates are metabolized to D-lactate and absorbed into the systemic circulation. Accumulation of D-lactate produces an anion gap metabolic acidosis in which the serum lactate level appears to be normal because the standard test for lactate is specific for L-lactate.

These patients typically seek medical attention after ingestion of a large carbohydrate meal that causes neurologic abnormalities consisting of confusion, slurred speech, and ataxia. Ingestion of low-carbohydrate meals and antimicrobial agents to decrease the degree of bacterial overgrowth are the principal treatments.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a metabolic condition characterized by the accumulation of acetoacetic acid and β-hydroxybutyric acid resulting from insulin deficiency and a relative or absolute increase in the glucagon concentration. The degree to which the anion gap is elevated depends on the rapidity, severity, and duration of the ketoacidosis and the status of the ECF volume. Although an anion gap acidosis is the dominant disturbance in diabetic ketoacidosis, a normal anion gap (hyperchloremic) acidosis often occurs in the earliest stages of ketoacidosis, when the ECF volume is near normal.

Confirmation of ketoacids can be achieved with the use of nitroprusside tablets or reagent strips. However, this test can be misleading in assessing the severity of ketoacidosis because it detects only acetone and acetoacetate, and it does not permit reaction with β-hydroxybutyrate.

Treatment of diabetic ketoacidosis involves the use of insulin and intravenous fluids to correct volume depletion. Deficiencies in K^+, magnesium (Mg^{2+}), and phosphate (PO_4^{3-}) are common, and these electrolytes are typically added to intravenous solutions.

Alcoholic Ketoacidosis

Ketoacidosis develops in patients with a history of chronic ethanol abuse, decreased food intake, and often a history of nausea and vomiting. Alcohol withdrawal, volume depletion, and starvation markedly increase the levels of circulating catecholamines and result in peripheral mobilization of fatty acids that is much larger in magnitude than that typically found with starvation alone. The metabolism of alcohol leads to an increase in the $NADH/NAD^+$ (i.e., balance between the reduced and oxidized forms of nicotinamide adenine dinucleotide), causing a higher ratio of β-hydroxybutyrate to acetoacetate. The nitroprusside reaction may be diminished by this redox shift despite severe ketoacidosis.

Glucose administration leads to the rapid resolution of the acidosis. Stimulation of insulin release leads to diminished fatty acid mobilization from adipose tissue and decreased hepatic output of ketoacids.

Ethylene Glycol and Methanol Poisoning

Ethylene glycol and methanol poisoning are characteristically associated with the development of a severe anion gap metabolic acidosis. Together with the appearance of the anion gap, an osmolar gap manifests and is an important clue to the diagnosis of ethylene glycol and methanol poisoning.

Metabolism of ethylene glycol by alcohol dehydrogenase generates various acids, including glycolic, oxalic, and formic acids. Ethylene glycol is a component of antifreeze and solvents and is ingested by accident or as a suicide attempt. The initial effects of intoxication are neurologic and begin with drunkenness, but they can quickly progress to seizures and coma. If left untreated, cardiopulmonary symptoms such as tachypnea, noncardiogenic pulmonary edema, and cardiovascular collapse may appear. Between 24 and 48 hours after ingestion, patients may develop flank pain and renal failure, which are often accompanied by abundant calcium oxalate crystals in the urine.

Methanol is also metabolized by alcohol dehydrogenase and forms formaldehyde, which is then converted to formic acid. Methanol is found in a variety of commercial preparations such as shellac, varnish, and de-icing solutions. As with ethylene glycol ingestion, methanol is ingested by accident or as a suicide attempt.

Methanol ingestion is associated with an acute inebriation, followed by an asymptomatic period lasting 24 to 36 hours. At this point, abdominal pain is caused by pancreatitis. Seizures, blindness, and coma may develop. The blindness results from the direct toxic effects of formic acid on the retina. Methanol intoxication is also associated with hemorrhage in the white matter and putamen, which can lead to the delayed onset of a Parkinson-like syndrome. Lactic acidosis, which is a feature of methanol and ethylene glycol poisoning, contributes to the elevated anion gap.

In addition to supportive measures, the therapy for ethylene glycol and methanol poisoning centers on reducing the metabolism of the parent compound and accelerating removal of the alcohol from the body. Fomepizole (4-methylpyrazole) is the agent of choice to inhibit the enzyme alcohol dehydrogenase and prevent formation of toxic metabolites.

Salicylate Poisoning

Aspirin (acetylsalicylic acid) poisoning leads to increased lactic acid production. The accumulation of lactic, salicylic, keto, and other organic acids leads to development of an anion gap metabolic acidosis. At the same time, salicylate has a direct stimulatory effect on the respiratory center. Increased ventilation