Acute ethanol toxicity

TERMINOLOGY

CLINICAL CLARIFICATION

- Acute ethanol toxicity results from ingesting ethanol faster than it can be metabolized by the liver and eliminated, leading to accumulation of ethanol and its metabolites in the blood
  - Result is intoxication with variable manifestations ranging from mild (altered sensorium, ataxia, incoordination) to severe (eg, stupor, respiratory depression, coma) with increasing blood ethanol concentrations

CLASSIFICATION

- *DSM-5* diagnostic criteria[1]
  - Recent ingestion of ethanol
  - Clinically significant problematic behavior or psychological changes (eg, inappropriate sexual or aggressive behavior, mood lability, impaired judgment) that developed during, or shortly after, ethanol ingestion
  - One (or more) of the following signs or symptoms developing during, or shortly after, ethanol use
    - Slurred speech
    - Incoordination
    - Unsteady gait
    - Nystagmus
    - Impaired attention or memory
    - Stupor or coma
  - Signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

DIAGNOSIS

CLINICAL PRESENTATION

- History
  - Common presenting patterns[2]
    - Traumatic injuries related to intoxication
      - Commonly related to motor vehicle accidents, nonfatal drowning, and violence
    - Medical complications related to intoxication
      - May include atrial fibrillation, pancreatitis, Mallory-Weiss tear, acute alcoholic hepatitis, dehydration, and electrolyte abnormalities
    - Intoxication alone
      - Accidental ingestion may occur in children
        - Ethanol-containing household products (eg, mouthwash, hand sanitizers, perfumes) account for most exposures
        - Unattended ethanol-containing beverages and medications (eg, cough and cold preparations) account for some exposures
      - Forced or coerced ingestion may occur in association with child sexual abuse or adolescent sexual assault
      - Cognitive impairment and dementia may be worsened by ingestion in elderly
  - Symptoms are dose dependent and are more pronounced when ethanol concentrations are increasing than when they are declining[3]
    - 1 to 2 standard drinks: mild euphoria, increased talkativeness, loosened inhibition, impaired judgment, relaxation, feeling of well-being, slowed motor performance, and impairment in some tasks requiring skill
    - 3 to 5 standard drinks: incoordination
    - 6 to 10 standard drinks: mood lability and overexpression (eg, sadness, anger), personality and behavioral changes, impaired cognition and memory, impaired judgment, altered perception of environment, slurred speech, marked incoordination, and ataxia
    - More than 10 standard drinks: nausea and vomiting (from pyloric spasm), marked slurring of speech, diplopia, and blackouts (amnesia)
      - Many more than 10 standard drinks: hypoventilation, coma, respiratory arrest
  - Individual variability exists in the dose necessary to produce various symptoms
    - Patients with ethanol tolerance may manifest few symptoms despite relatively high blood ethanol concentration; in contrast, ethanol-naive patients may manifest symptoms at lower blood ethanol concentrations (eg, coma in young child or teen with concentration of 100-200 mg/dL)[4]
    - Constellation of possible symptoms of intoxication varies among individual patients[5]

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- Pattern and characteristics of mental status changes are often similar in a given person from one intoxication episode to another
  - Markedly uncharacteristic mental status changes from previous episodes of intoxication may indicate additional pathology (eg, occult head injury, electrolyte abnormality, concomitant use of additional illicit drugs)
- Many patients seeking care for acute ethanol intoxication present with concomitant medical problems related to excessive long-term ethanol use or alcohol use disorder
  - Denial or minimization of intake and maladaptive ethanol use patterns are common; close contacts (eg, significant other, roommate) may provide more accurate account of ethanol use
  - Patients also often deny or minimize impaired motor and cognitive functions during intoxication
- Coingestion of another drug, or several drugs, is not uncommon in intoxicated patients presenting for emergent care[6]

- Physical examination
  - Signs of acute mild to moderate intoxication
    - Ethanol smell on breath
    - Conjunctival injection
    - Slurred speech, incoordination, ataxia, and nystagmus
    - Hyperreflexia
    - Impaired sensation
    - Impaired attention
    - Impaired memory
      - Temporary anterograde amnesia (blackout) results from a rapid increase in blood ethanol concentration[3]
      - Patient may not recall any events that happened during intoxication (en bloc amnesia) or may recall only parts of the episode (fragmentary amnesia)[3]
    - Tachycardia
    - Signs of volume depletion (eg, tacky or dry mucous membranes, lack of tears, prolonged capillary refill time)
    - Significant skill deficits (eg, inability to walk, talk, or drive), but preserved consciousness
  - Signs of severe intoxication
    - Impairment or absence of gag reflex
    - Hypoventilation
    - Hypothermia
    - Hypotension secondary to peripheral vasodilation and/or volume depletion
    - Respiratory depression and arrest
    - Stupor or coma
  - Seizure activity
    - Usually a consequence of ethanol-related hypoglycemia; common adrenergic symptoms associated with hypoglycemia are often absent (eg, diaphoresis)[4]
  - Less prevalent manifestations that may occur during episode of heavy drinking
    - Abnormal heart rhythms (eg, atrial fibrillation, ventricular rhythms); these may occur in patients without other evidence of heart disease or in patients with underlying cardiac pathology
  - Signs suggestive of long-term ethanol use
    - Prominent capillaries (eg, nose, cheeks)
    - Spider nevi
    - Telangiectasias
    - Palmar erythema
    - Hepatomegaly from fatty liver, alcoholic hepatitis, or hepatic cirrhosis
    - Hypertension
    - Findings consistent with cardiomyopathy (eg, left ventricular heart failure with mitral regurgitation)

Manifestations of alcohol intoxication based on blood ethanol concentration.

Blood alcohol concentration	Approximate alcohol consumption	Manifestations
Less than 50 mg/dL	1 to 2 standard drinks	Mild euphoria, increased talkativeness, relaxation, feeling of well-being, loosened inhibition, impaired judgment, slowed motor performance, impairment in some tasks requiring skill
More than 50 mg/dL	3 to 5 standard drinks	Impaired sensation, incoordination

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More than 100 mg/dL	6 to 10 standard drinks	Mood lability, personality and behavioral changes, impaired cognition and memory, impaired judgment, altered perception of environment, prolonged reaction time, slurred speech, hyperreflexia, marked incoordination, ataxia, mild nystagmus
More than 200 mg/dL	More than 10 standard drinks	Nausea, vomiting, marked nystagmus, diplopia, alcoholic blackouts (amnesia), marked slurring of speech, increased risk of aspiration
More than 300 mg/dL		Hypoventilation, diminishing ability to protect and maintain airway, hypothermia, cardiac arrhythmia
More than 400 mg/dL		Coma, absent gag reflex, respiratory arrest, hypotension, death
Standard drink contains about 10 to 14 g of ethanol (depending on exact ethanol percentage in each beverage/product); expected increase in blood ethanol concentration after 1 standard drink is about 15 to 25 mg/dL in a 70-kg man.		

Data from Jung YC et al: Alcohol: intoxication and poisoning--diagnosis and treatment. Handb Clin Neurol. 125:115-21, 2014; Vonghia L et al: Acute alcohol intoxication. Eur J Intern Med. 19(8):561-7, 2008; Vale A: Alcohols and glycols. Medicine. 44(3):128-32, 2016; and Department of Health and Human Services: Appendix 9: alcohol. In: Dietary Guidelines for Americans, 2015-2020. HHS website. Updated 2015. Accessed March 1, 2019. https://health.gov/dietaryguidelines/2015/guidelines/appendix-9/

CAUSES AND RISK FACTORS

- Causes
  - Pharmacology
    - Ethanol (ethyl alcohol) is a central nervous system depressant (interferes with cortical functioning in small doses and medullary functioning in high doses) and a peripheral vasodilator[4]
    - Common ethanol-containing substances
      - Ethanol-containing beverages
        - Standard drink contains about 10 to 14 g of ethanol (about 0.4-0.6 fl oz), depending on exact ethanol percentage in each beverage/product; expected increase in blood ethanol concentration after 1 standard drink is about 15 to 25 mg/dL in a 70-kg man[3,7,4,8]
        - One standard drink usually equates to about 1.5 oz of 80 proof liquor (40% ethanol), 5 oz of wine (12% ethanol), or 12 oz of beer (5% ethanol)[7]
      - Powdered ethanol (eg, Palcohol)
        - Palcohol when mixed with 200 mL of water results in 55% ethanol by volume (10% ethanol by weight)[6]
          - Many US states have adopted legislation banning sale of such products[9]
      - Medication preparations
        - Cough and allergy remedies may contain up to 16% ethanol[6]
        - Cough remedies may contain up to 25% ethanol[6]
      - Food extracts
        - Vanilla extract contains no less than 35% ethanol by US law[10]
      - Household products
        - Glass cleaners may contain up to 10% ethanol[6]
        - Hand sanitizer may contain up to 62% ethanol[6]
      - Cosmetics and personal care items
        - Mouthwash may contain up to 25% ethanol[6]
        - Perfumes and colognes may contain up to 95% ethanol[6]
        - Aftershave products may contain up to 80% ethanol[6]
    - Factors affecting extent of intoxication[6,3]
      - Volume ingested, ethanol concentration of the ingested liquid, and time course of ingestion
      - State of fasting
        - Fasting results in increased blood ethanol concentration
        - Food in stomach delays absorption, resulting in lower blood ethanol concentration and delayed peak concentration
      - Sex: gastric alcohol dehydrogenase metabolism is lesser in females, resulting in increased absorption and blood ethanol concentrations
      - Individual body weight and composition: increased adiposity and decreased lean body weight result in higher blood ethanol concentrations
      - Long-term ethanol use
        - Heavy drinkers with significant tolerance manifest fewer signs and symptoms of intoxication at any given blood ethanol concentration
        - Patients with severe liver disease may have decreased rates of ethanol metabolism that correlate with severity of hepatic damage

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- Genetic susceptibility may play a role in differences in individual manifestations of intoxication
- Medications and coingestion of additional substances may have variable effects on blood ethanol concentration (ie, either augment effects or antagonize effects)

– Absorption
- Most ingested ethanol is absorbed in small intestine;[4] stomach absorbs about 10%[3]
- Absorption is rapid; peak serum levels are usually achieved between 30 and 90 minutes[3]

– Metabolism
- Substantial variability exists in rates of ethanol degradation among individual patients; consumption of ethanol exceeding rate of degradation and elimination results in accumulation and manifestations of intoxication[5]
  - In general, patients can metabolize 1 standard drink per hour without ethanol accumulation in blood and resultant intoxication
  - People ***without*** heavy long-term ethanol use (ie, those who are nontolerant or ethanol-naive) metabolize and eliminate ethanol at a rate of about 15 mg/dL/hour[5]
  - People ***with*** heavy long-term ethanol use metabolize and eliminate ethanol faster, at rates up to 25 mg/dL/hour[5]
- Ethanol metabolism involves 2 enzymes: alcohol dehydrogenase (converts ethanol to acetaldehyde) and aldehyde dehydrogenase (converts acetaldehyde to acetic acid)
- Gastric alcohol dehydrogenase is responsible for about 10% of metabolism before absorption (ie, first-pass metabolism)[8]
  - Young women have lower gastric alcohol dehydrogenase activity[4]
- Liver enzymatic pathways account for remaining 90% of metabolism[8]
  - Liver alcohol dehydrogenase contributes to most hepatic metabolism (about 90%)[8]
    - Diminished activity of alcohol dehydrogenase in young children may be responsible for decreased ability to metabolize ethanol, resulting in rapid increase in blood ethanol concentration and toxicity[11]
  - Microsomal ethanol-oxidizing system, another hepatic enzyme system, accounts for a minority of hepatic metabolism (about 8%-10%)[8]
    - Activity of this enzyme system can be induced by long-term ethanol use and enzyme-inducing drugs[4]
  - Catalase is a very minor contributor to hepatic metabolism (about 0%-2%)[8]

– Elimination
- Most ingested ethanol is metabolized to acetaldehyde and acetate, eventually resulting in carbon dioxide and water; remainder is excreted unchanged in the urine and (to a lesser extent) in the breath and through the skin[4]

○ Toxic dose
– Toxic dose varies[12,13] but has been defined as 5 g/kg in adult and 3 g/kg in child[6]
– Symptoms are usually related to blood ethanol concentration
- Increased risk of respiratory depression and arrest may occur with concentrations exceeding 300 mg/dL[8]
- Lethal dose varies
  - Death attributable to acute intoxication generally occurs with concentrations exceeding 500 mg/dL[8]
  - Death attributable to acute intoxication in nontolerant or ethanol-naive patients may occur at lower concentrations (eg, 300-500 mg/dL)[8]
  - Fatal complications may occur at much lower blood ethanol concentrations in children (less than 50 mg/dL)[6]

- Risk factors and/or associations

○ Age
– Children and elderly people are at highest risk of intoxicating effects of ethanol compared with other age groups[6]
– Children may be at increased risk for profound effects (eg, hypoglycemia, hypothermia, coma) after ingesting relatively small amounts of ethanol[14]

○ Other risk factors/associations
– Risk factors for development of hypoglycemia associated with acute intoxication
- Young age[4]
- Fasting state[4]
- Vigorous exercise[4]
- Chronic malnutrition[4]

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools

○ Intoxication is diagnosed by clinical presentation and *DSM-5* criteria
○ Obtain the following ancillary tests at presentation:
– Bedside glucose measurement in all intoxicated patients, all exposed children, and patients with mental status depression[5]
– Electrolyte levels in patients with moderate to severe intoxication and in patients requiring IV fluid hydration[15]

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- Assessment of blood ethanol concentration (either directly or indirectly) is commonly performed in patients with moderate to severe manifestations, in children,[2] and in patients with mental status depression and unknown history of ethanol exposure[6]
  - Direct blood ethanol concentration measurement
    - May confirm diagnosis of ethanol exposure and deem alternative alcohol exposure less likely (eg, exposure to ethylene glycol, methanol, or isopropyl alcohol); however, coingestion of other alcohols can occur[3]
    - Obtain in patients for whom legal ramifications are evident (eg, concern for child abuse, adult operating machinery or vehicle)[3]
  - Breath analysis
    - Less invasive but less accurate than blood ethanol concentration measurement
  - Serum osmolality and osmolal gap
    - May be used as an indirect measure of blood ethanol concentration when direct measurement is unavailable
- Assessment of acid-base status in severely intoxicated patients (eg, those with hypothermia, in shock, or in coma)[4]

- Remember to evaluate for potential alcohol-related disease and non–alcohol-related conditions in patients with suspected or diagnosed acute ethanol intoxication[8]
  - Exclude occult trauma as needed
    - Order head CT when neurologic signs are present, head trauma is suspected, and/or mental status is not improving as anticipated[3]
    - Maintain low threshold for cervical spine imaging; intoxicated patients are not candidates for clearing of cervical spine clinically
  - Consider possibility of coingestion, based on history and exam
  - Additional studies may be indicated to exclude alternative diagnosis, depending on individual presentation, such as the following:
    - Other substance-related mental status depression (eg, naloxone trial for possible opioid toxicity)
    - Central nervous system infections such as encephalitis and meningitis (eg, cerebrospinal fluid analysis)
    - Encephalopathic states (eg, liver function testing)
  - Other studies that may be indicated based on clinical presentation
    - Chest radiograph to assess for aspiration in patients with respiratory symptoms or vomiting plus mental status depression
    - ECG to assess for arrhythmia in patients with abnormal cardiac examination findings
    - Sexual assault or abuse evaluation if concerns exist
- Incidental findings consistent with excessive long-term ethanol use[3]
  - Elevated mean corpuscular volume, γ-glutamyltransferase level, and carbohydrate-deficient transferrin level
  - Anemia, neutropenia, and thrombocytopenia
- Obtain routine tests after intentional ingestion with intent for self-harm
  - Serum acetaminophen concentration
  - Urine/serum hCG level in women of childbearing age
  - Head CT with any significant unexpected alteration in sensorium, prolonged or focal seizures, signs of increased intracranial pressure, or focal neurologic deficit

- Laboratory
  - Measurement or estimation of blood ethanol concentration
    - Limitations
      - Values do not necessarily correlate with clinical presentation[3]
      - Values lack predictive ability regarding clinical severity and outcome[3]
      - Values often do not influence decisions on management or disposition[6]
    - Most common tests
      - Blood ethanol concentration (direct measurement)
        - Legal intoxication level above which penalties may be imposed for operating a vehicle or machinery in most states in the United States is 80 mg/dL (or 0.08 g/dL)[3]
        - Absence of significant manifestations (eg, motor impairment, cognitive impairment) with concentration more than 100 mg/dL suggests tolerance and long-term ethanol use[3]
        - Severe intoxication manifestations are usually associated with concentrations more than 300 mg/dL[4]
      - Indirect/proxy measurements
        - Breath ethanol concentration
          - Analysis is less reliable than blood concentration analysis; results are often slightly lower than blood concentration[3,6]
          - Testing within 15 to 20 minutes of last drink and with presence of vomitus in mouth may cause false elevation; false-negatives are rare[6]

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- Serum osmolality and osmolal gap
  - Serum osmolality
    - Measure of total molal concentration of all osmotically active solutes in plasma [16]
    - General reference range for serum osmolality is 285 to 290 mOsm/L [17]
    - Abnormally high measured serum osmolality not explained by increased level of urea, glucose, or sodium indicates accumulation of low-molecular-weight osmotically active substances in plasma [17]
    - Serum osmolality rises about 22 mOsm/L for every 100 mg/dL increment in blood ethanol concentration [8]
  - Osmolal gap
    - Screening test for presence of unmeasured, osmotically active substances in serum [16]
    - Osmolal gap = measured serum osmolality – calculated osmolality
    - When ethanol concentration is not available, calculated osmolality = (2 × Na) + (BUN/2.8) + (glucose/18)
    - Reference range for osmolal gap can vary, but generally, values more than 10 mOsm/L are considered elevated [18]
    - Causes of an elevated osmolal gap can include alcohols (eg, ethanol, ethylene glycol, methanol, isopropanol, propylene glycol), glycerol, mannitol, acetone, sorbitol, ketoacidosis, and unknown osmotically active solutes in critical illness (eg, multiorgan failure, renal failure, circulatory shock) [19, 20]
    - Serum osmolal gap out of proportion to blood ethanol concentration suggests presence of additional unmeasured osmotically active substance (eg, coingestion of ethanol plus another alcohol)
- Blood glucose level
  - Disturbance typically occurs within 6 to 36 hours of ingestion [4]
  - Hypoglycemia is most common in children and adolescents, particularly children younger than 5 years [2, 4]
    - Development of hypoglycemia in children does not appear to be dose dependent [6]
    - Children can develop hypoglycemia with blood ethanol concentrations less than 30 mg/dL [6]
  - Other risk factors for development include vigorous exercise, fasting state, and chronic malnutrition [4]
- Serum electrolyte levels
  - Abnormalities may include hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia [2, 8]
- Acid-base disorders [4]
  - May occur with severe intoxication
  - Respiratory acidosis is more common than metabolic acidosis
  - Metabolic alkalosis may develop with persistent vomiting and dehydration

- Imaging
  - Head CT
    - Clinically important signs of trauma may include evidence of skull fracture, subdural hematoma, epidural hematoma, and subarachnoid bleeding
    - Incidental findings consistent with long-term ethanol use include brain atrophy with ventricular enlargement and widened cortical sulci most pronounced in prefrontal cortex [3]
- Other diagnostic tools
  - *DSM-5* diagnostic criteria for alcohol (ethanol) intoxication [1]
    - Recent ingestion of alcohol (ethanol)
    - Clinically significant problematic behavior or psychological changes (eg, inappropriate sexual or aggressive behavior, mood lability, impaired judgment) that developed during, or shortly after, alcohol (ethanol) ingestion
    - One (or more) of the following signs or symptoms developing during, or shortly after, alcohol (ethanol) use:
      - Slurred speech
      - Incoordination
      - Unsteady gait
      - Nystagmus
      - Impairment in attention or memory
      - Stupor or coma
    - Signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance

DIFFERENTIAL DIAGNOSIS

- Most common
  - Ethylene glycol toxicity [21, 16]
    - Results from ingestion of products containing ethylene glycol (eg, antifreeze, brake fluid, radiator coolant, deicing solution)
    - Presentation is often similar with signs of altered mental status, nystagmus, ataxia, slurred speech, euphoria, vomiting, and increased osmolal gap

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- Ethylene glycol is odorless; patients presenting with acute ethanol ingestion usually present with distinct breath odor
- Severe metabolic acidosis with increased anion gap suggests ethylene glycol ingestion rather than isolated ethanol ingestion; ethanol may cause mild-moderate acidosis, but a severe increased anion gap metabolic acidosis is not typical
- Crystalluria and hypocalcemia commonly develop over time in patients with ethylene glycol toxicity; renal failure may result and suggests ethylene glycol ingestion rather than isolated ethanol ingestion
- Diagnosis is typically based on a high index of suspicion with proper interpretation of adjunct laboratory diagnostics (eg, presentation consistent with alcohol intoxication, increased osmolal gap, severe increased anion gap metabolic acidosis, crystalluria, hypocalcemia, absence of detectable serum ethanol concentration) and improvement with proper treatment (eg, antidote fomepizole)
- Serum ethylene glycol concentration confirms diagnosis but is of limited use given need for reference laboratory testing (lengthy turnaround time)

- Methanol toxicity[16, 22]
  - Results from ingestion of methanol-containing products (eg, denatured alcohol, automotive fluids, embalming fluids, paints, varnishes, wood stains, lacquer, paint thinner)
  - Presentation is often similar with signs of altered mental status, nystagmus, ataxia, slurred speech, euphoria, vomiting, and increased osmolal gap
  - Methanol ingestion may produce an odor on breath that is similar to that of ethanol but fainter (unreliable sign)
  - Characteristically toxicity results in prominent, latent (after 6-30 hours) ocular symptoms including visual impairment, altered color perception, snowfield vision, and possibly blindness[16]
  - Diagnosis is typically based on a high index of suspicion with proper interpretation of adjunct laboratory diagnostics (eg, presentation consistent with alcohol intoxication, increased osmolal gap, severe increased anion gap metabolic acidosis, prominent ocular findings, absence of detectable serum ethanol concentration) and improvement with proper treatment (eg, antidote fomepizole)
  - Serum methanol concentration confirms diagnosis but is of limited use given need for reference laboratory testing (lengthy turnaround time)
- Isopropyl alcohol toxicity[23, 24]
  - Isopropyl alcohol (isopropanol) is the common solvent in household rubbing alcohol
  - Initial manifestations can mimic those of ethanol toxicity with inebriation, vomiting, central nervous system depression, and hyperosmolarity (ie, increased osmolal gap); notably, development of acidosis is absent in isolated isopropyl alcohol ingestion
  - Clinical clues to isopropyl alcohol intoxication are fruity breath odor (ketones) with substantial ketonemia and ketonuria without acidemia; elevated blood and urine acetone concentrations (ie, strong positive nitroprusside reaction) without elevation of β-hydroxybutyrate levels is characteristic
  - Very high acetone concentrations can falsely elevate serum creatinine level (whereas BUN level remains within reference range) and result in false-positive ethanol breath test result
  - Serum isopropanol concentration confirms diagnosis but is of limited utility given need for reference laboratory testing (lengthy turnaround time); management parallels that of acute ethanol ingestion
- Benzodiazepine toxicity
  - Presentation is practically identical to that of acute ethanol toxicity (eg, central nervous system depression, slurred speech, ataxia)
  - Distinguishing feature in patients with isolated, acute benzodiazepine toxicity is that smell of ethanol on breath is absent
  - Flumazenil can reverse toxic effects of benzodiazepines
    - Use with caution owing to potential for adverse effects, including:
      - Increased intracranial pressure
      - Ventricular dysrhythmias
      - Seizures in patients with epilepsy or coingestion associated with lowering of seizure threshold
      - Acute benzodiazepine withdrawal
  - Differentiate and diagnose by clinical presentation; detection of benzodiazepine on drug screen provides evidence of recent exposure
- Opioid toxicity
  - May present similarly with drowsiness, inebriation, mental status depression, and hypothermia
  - Additional common signs of overdose include miosis, bradycardia, and hypotension
  - Naloxone may reverse manifestations
  - Differentiate and diagnose by clinical presentation and clinical course; detection of opioid on drug screen provides evidence of recent exposure

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- Wernicke-Korsakoff syndrome[3]
  - Both conditions are a consequence of thiamine (vitamin B_1) deficiency and are diagnosed based on clinical presentation
  - Patients with alcohol use disorder are at increased risk of vitamin B_1 deficiency secondary to poor nutrition, compromised gastrointestinal absorption, reduced B_1 storage, and impaired utilization of B_1
  - Wernicke encephalopathy
    - Acute and reversible consequence of thiamine deficiency
    - May present similarly with acute mental status changes (eg, apathy, inattention, confusion, coma), ataxia, and ocular abnormalities (eg, nystagmus, ophthalmoplegia)
    - Dramatic improvement is often noted with parenteral thiamine replacement
    - Diagnosis is based on clinical criteria (at least 2 of 4 conditions in a person with known long-term ethanol use: nutritional deficiency, ocular findings, ataxia, and/or mental status changes)[5]
  - Korsakoff syndrome
    - Untreated Wernicke encephalopathy can progress to Korsakoff syndrome which is characterized by disproportionate impairment in memory relative to other aspects of cognitive functioning
    - May present similarly to ethanol intoxication with amnesia
    - Amnesia associated with Korsakoff syndrome is global and chronic, whereas amnesia (blackout) associated with ethanol intoxication is temporary
    - Diagnosis is clinical
- Hepatic encephalopathy[3]
  - Presents with confusion and change in personality mimicking ethanol intoxication
  - Usually precipitated by an event such as gastrointestinal bleed, electrolyte abnormalities, dehydration, infection, excessive use of central nervous system depressant medication, or ethanol intoxication
  - Severe encephalopathy may progress to cerebral edema, increased intracranial pressure, and death
  - Unlike with ethanol intoxication, asterixis is often noted on examination; laboratory tests often find elevated liver enzyme levels and ammonia levels
  - Diagnosis is based on clinical presentation, clinical course, and laboratory values
- Central nervous system infection
  - Meningitis and encephalitis may mimic ethanol intoxication with mental status changes, vomiting, and seizures
  - In contrast with patients with ethanol intoxication, patients with central nervous system infection most often present with fever and meningeal signs
  - Diagnosed with lumbar puncture and cerebrospinal fluid analysis
- Beer potomania[5]
  - Condition results from ethanol-induced hyponatremia in malnourished people with long-term ethanol use
  - Presents similarly to ethanol intoxication with altered mental status and seizures
  - Concomitant findings in patients with beer potomania include low potassium levels, euvolemic state (with normal BUN and creatinine levels), low serum osmolality, and low urine sodium level
  - Differentiate from acute intoxication by presence of hyponatremia
  - Diagnosis is confirmed by excluding other causes of hyponatremia in a person with long-term ethanol use

TREATMENT

GOALS

- Provide effective resuscitation when indicated
- Provide symptomatic care; no antidote is available for ethanol intoxication; replace thiamine when indicated
- Treat concomitant conditions such as hypoglycemia, dehydration, vomiting, electrolyte abnormalities (eg, hyponatremia, hypomagnesemia), seizures, and agitation

DISPOSITION

- Admission criteria
  - Admit children with acute ethanol toxicity for close monitoring for hypoglycemia and further management
  - Indications for admission of adults[15]
    - Persistently abnormal vital signs (eg, hypotension)
    - Persistently abnormal mental status with or without an identifiable cause
    - Respiratory depression
    - Overdose with intended self-harm
    - Concomitant serious trauma
    - Consequential ethanol withdrawal
    - Associated serious disease process (eg, gastrointestinal bleed, pancreatitis)

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- Complication requiring ongoing management (eg, dehydration, hypoglycemia)
- Criteria for ICU admission
  - Respiratory failure, severe withdrawal, and some concomitant conditions (eg, sepsis, intracranial hemorrhage) require ICU level of care [25]
    - Risk factors for ICU requirement include hypoglycemia, fever, hypothermia, hypoxia, hypotension, sedation requirement, and tachycardia
- Recommendations for specialist referral
  - Consult poison control center and/or medical toxicologist for management concerns
  - Consult substance use/addiction medicine specialist or mental health provider for diagnostic and treatment recommendations regarding concerns about alcohol use disorder

TREATMENT OPTIONS

- Treatment is multifaceted, addressing several medical issues
- Resuscitation
  - Protect airway; provide respiratory and cardiovascular support per standard protocols
- Dehydration and hypovolemia
  - Treat with IV fluid bolus and ongoing infusion
  - Consider IV solution with dextrose, magnesium, folate, thiamine, and multivitamins per institutional protocol when IV fluids are required [8]
  - IV fluid administration does not alter blood ethanol clearance [6]
- Metabolic abnormalities
  - Thiamine deficiency
    - Consider thiamine replacement in patients at risk for deficiency: those with malnutrition, long-term ethanol use, alcohol use disorder, or (in adults) hypoglycemia [4]
  - Hypoglycemia
    - Treat with oral glucose if possible; IV dextrose bolus followed by infusion and close monitoring of serum glucose levels may be required
    - Replace thiamine (B_1) in older patients (probably not necessary in children) or malnourished patients when bolusing with glucose; give thiamine dose via parenteral route [5]
    - Note that hypoglycemia is usually unresponsive to glucagon [4]
  - Electrolyte abnormalities
    - Correct in standard way per institutional protocol
    - Do not correct hyponatremia too rapidly, given increased risk for osmotic demyelination syndrome (ie, central pontine and extrapontine myelinolysis) in patients with alcohol use disorder
- Neurologic abnormalities
  - Seizures
    - Treat hypoglycemia when present
    - Treat per standard protocol beginning with benzodiazepine (eg, lorazepam) administration
  - Agitation and restlessness
    - Avoid use of physical restraints owing to risk of traumatic injury and rhabdomyolysis in acutely agitated patients [8]
      - Temporary use may be necessary when condition is extreme
    - First line pharmacotherapy is typical antipsychotics (eg, haloperidol); [8, 2] ketamine may be an alternative [26, 27]
    - Maintain caution with any medication with potential to cause respiratory depression (eg, benzodiazepines) [15]
- Other symptomatic care
  - Vomiting
    - Place patient in lateral position and provide gentle suction as needed to clear oropharynx and lower risk of aspiration [3]
    - Consider antiemetic administration (eg, ondansetron) when contraindications are absent [3]
  - Hypothermia
    - Treat in standard fashion with external warming measures (eg, warm blankets, external warming system, radiant heat, heat lamps)
- Hemodialysis
  - May be considered in the following urgent circumstances: [4]
    - Ethanol concentration more than 750 mg/dL
    - Severe metabolic acidosis
    - Severely impaired liver function
- Drug therapy
  - Thiamine
    - Several dosing regimens are available

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- Give thiamine before any glucose administration to avoid precipitating Wernicke encephalopathy [28]
- To prevent Wernicke encephalopathy:
  - Oral
    - Vitamin B_1 (Thiamine) Oral tablet; Adults: 100 mg PO once daily for 3 to 5 days. [29]
  - IV
    - Vitamin B_1 (Thiamine Hydrochloride) Solution for injection; Adults: 100 mg IV once daily for 3 to 5 days. [30]
- To treat Wernicke encephalopathy based on suggestive symptoms:
  - Vitamin B_1 (Thiamine Hydrochloride) Solution for injection; Adults: 500 mg IV every 8 hours for 5 days, followed by 250 mg IV once daily for 3 to 5 days depending on response. [30]

- IV solution with dextrose, magnesium, folate, thiamine, and multivitamins
  - Premixed IV solution of 1:1 5% dextrose and 0.45% sodium chloride, 2 gm of magnesium sulfate, 1 mg of folate, 100 mg of thiamine, and multivitamins. [8]
- Haloperidol
  - May be used to diminish agitation in violent or agitated patients [8]
  - Maintain caution because interactions between medications with sedative properties and ethanol may precipitate respiratory depression and hypotension [8]
  - Haloperidol Lactate Solution for injection; Adults: 2 to 5 mg IM single dose initially; use if oral therapy is not appropriate; may administer as frequently as 1 hour intervals if needed, though dosing every 4 to 8 hours satisfactory for most patients. Max: 20 mg/day IM. Geriatric patients may require a lower dose and gradual titration. Use the lowest effective dose in all patients. Convert to oral therapy as soon as clinically indicated. SWITCHING TO ORAL THERAPY: In general, the total IM dose given the preceding 24 hours may be used as the initial daily PO dosage. Give the first oral dose within 12 to 24 hours following the last IM dose.
- Dextrose infusion
  - Dextrose 10% Solution for Injection; Neonates, Infants, and Children: 2 to 3 mL/kg bolus, followed by continuous infusion rate beginning at 4 to 8 mg/kg/minute.
  - Dextrose Solution for injection; Adults: 10 to 25 grams/dose (i.e., 20 to 50 mL of a dextrose 50% injection solution) IV to restore blood glucose concentrations. In severe cases, repeat doses may be needed. Subsequent continuous IV infusion of dextrose 10% injection may be necessary to stabilize serum glucose concentrations in some individuals.
- Other glucose supplementation
  - Glucose oral tablets; Children: 0.3 g glucose per kg body weight (5 to 20 g depending on the child's body weight).

- Nondrug and supportive care
  - Psychiatric evaluation
    - Indicated for all patients intending self-harm
  - Social service evaluation
    - Recommended for all children presenting with acute intoxication to ensure safety of living environment and to assess competency of caregiver
  - Screen for heavy long-term ethanol use and alcohol use disorder before discharge
  - Evaluate for risk of alcohol withdrawal before discharge; provide referrals for medication-assisted treatment as indicated
- Comorbidities
  - Alcohol use disorder
    - Patients are at heightened risk for vitamin deficiencies and withdrawal when presenting with acute ethanol intoxication
      - Maintain low threshold for thiamine replacement and folate supplementation
      - Assess risk for withdrawal and recommend close follow-up to assess need for medically assisted withdrawal treatment
    - Brief intervention after clearing of sensorium is the first step to define and formulate treatment plan for alcohol use disorder; refer for appropriate intensive pharmacologic, psychiatric, and psychosocial treatment of alcohol use disorder
- Special populations
  - Children
    - More susceptible to hypoglycemia than other age groups; young children are particularly vulnerable to hypoglycemia even when not much ethanol was ingested
    - Heightened monitoring and more aggressive treatment of hypoglycemia may be warranted

MONITORING

- Monitoring for symptomatic patients
  - Repeat clinical assessments of mental status and neurologic examination frequently [3]

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- Mental status
  - Acute manifestations of ethanol intoxication (eg, slurred speech, altered mental status, ataxia) can mask or mimic comorbid conditions; improvement in manifestations (eg, better mental status, cessation of vomiting) is expected after acute intoxication
  - Failure of mental status to improve and persistent vomiting raise suspicion for occult traumatic central nervous system injury or additional comorbid medical condition; further investigation may be indicated
- Hypoglycemia
  - It is typical to monitor blood glucose levels at least hourly in adult patients with hypoglycemia and to adjust glucose infusion rate accordingly[4]
  - Children in particular require close monitoring for hypoglycemia
    - A reasonable monitoring schedule is to check blood glucose level hourly until stable, and then every 4 hours for a total of at least 24 hours
- Monitoring of abnormal laboratory findings
  - Follow up on electrolyte abnormalities requiring treatment with repeated laboratory tests as appropriate
    - Choose frequency of monitoring based on severity of abnormality, age of patient, and clinical course

- Discharge criteria
  - Reassess and reexamine for possibility of occult trauma, including brain trauma and cervical spine injury, before discharge when sensorium is clear
  - Screen for heavy long-term ethanol use and alcohol use disorder before discharge; use a validated screener such as the AUDIT-C short questionnaire (Alcohol Use Disorders Identification Test–Consumption) or the CAGE questionnaire (cut down, annoyed, guilty, eye opener)[8]
    - If screening result is positive then administer a second tier screening tool such as the full AUDIT questionnaire and assess for *DSM-5* alcohol use disorder criteria; perform brief behavioral intervention and refer patients with suspected alcohol use disorder for formal, structured treatment
    - If screening result is negative and alcohol use disorder is not suspected then perform brief alcohol counseling intervention with the goal of reducing harm by reducing harmful drinking practices
  - Generally accepted discharge criteria include ability to walk without difficulty, tolerate oral intake, and demonstrate clear and appropriate thought process in patients who are not a danger to themselves or others[6]
    - Ideally patients are discharged to a protected environment under the supervision of another sober and competent adult[15]
- Monitoring of asymptomatic children after ingestion
  - Monitor for development of clinical manifestations for 2 to 4 hours after ingestion, in consultation with poison control center or medical toxicologist
  - Confirm maintenance of euglycemia with repeated serum glucose measurement before discharge

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Dehydration
  - May occur secondary to gastrointestinal losses, ethanol-related diuresis, and diminished intake
- Electrolyte disorders
  - Hyponatremia
    - May occur in association with acute intoxication, particularly in people with long-term ethanol use[5]
    - Causes are diverse and may include hypovolemia, beer potomania, pseudohyponatremia (hypertriglyceridemia, hyperproteinemia), syndrome of inappropriate antidiuretic hormone, cardiomyopathy, cirrhosis, and cerebral salt-wasting syndrome[5]
  - Hypomagnesemia
    - Present in up to 7% of acutely intoxicated patients and up to 30% with alcohol use disorder[5]
    - Causes in people with long-term ethanol use are diverse; they include dietary deficiency, malabsorption, increased urinary excretion, ketosis, and vitamin D deficiency[5]
- Hypoglycemia
  - Children are at highest risk regardless of nutritional status; derangement may occur several hours after ethanol ingestion
  - Much less common in adults; malnutrition and fasting state place adults at higher risk
  - Development does not appear to be related to dose of ethanol or blood ethanol concentration
- Alcoholic ketoacidosis[5]
  - Patients with alcoholic ketoacidosis generally present with the triad of abdominal pain, nausea, and vomiting
    - Typical scenario is a recent alcoholic binge causing abdominal pain, which causes cessation of drinking, subsequently leading to the alcoholic acidosis, which causes nausea and vomiting

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- Laboratory findings include elevated anion gap acidosis, ketonuria, and occasionally ketoacidemia
  - β-hydroxybutyrate is present in much higher concentrations than in diabetic ketoacidosis
- Treat with isotonic volume expansion with dextrose-containing fluids, such as 5% dextrose in normal saline

- Pulmonary complications
  - Aspiration
    - May occur secondary to decreased airway sensitivity to foreign bodies, impaired mucociliary clearance, respiratory depression, and diminished gag reflex[8]
    - Aspiration may be associated with increased risk for respiratory infection (eg, bronchitis, pneumonia)[8]
- Gastrointestinal complications
  - Mallory-Weiss tear
    - Presents with hematemesis secondary to longitudinal laceration at the gastroesophageal junction; may occur with forceful retching or vomiting[3]
  - Esophagitis, gastritis, and gastric ulcers
    - Secondary to direct mucosal irritation caused by ethanol[3]
  - Pancreatitis
    - Secondary to inflammation of pancreas caused by heavy drinking[3]
  - Dysfunctional gastrointestinal motility
    - May result in diarrhea[8]
  - Acute alcoholic hepatitis
    - Acute ethanol intoxication may induce acute hepatitis, particularly in patients with comorbid alcohol use disorder or alcoholic cirrhosis[8]
- Atrial and ventricular arrhythmias
  - May occur after acute intoxication without underlying comorbid cardiac disease[31]
  - May further worsen underlying cardiac impairment or acutely increase risk for lethal arrhythmia in patients with myocardial infarction[31]
  - New-onset atrial fibrillation after ethanol consumption (referred to as holiday heart syndrome) is not uncommon[31]
- Sleep abnormalities during episode of intoxication
  - Exacerbation of sleep apnea[3]
    - Secondary to relaxation of pharyngeal musculature
  - Sleep fragmentation and nonrestorative sleep[3]
- Peripheral neuropathy
  - Patients with long-term ethanol use may experience manifestations of peripheral neuropathy after an intoxicating episode[3]
  - Symptoms often include bilateral paresthesias with limb numbness, tingling, and burning sensations; symptoms are usually more pronounced in a distal (rather than proximal) distribution[3]
- Transient hormonal changes associated with acute ethanol intoxication (***none require specific medical intervention***)
  - Vasopressin secretion inhibition with resultant diuresis[3]
  - Increase in adrenocorticotropic hormone and cortisol levels; decrease in thyroxine and triiodothyronine levels[3]
- Suicide or suicide attempts
  - Highly associated with acute ethanol intoxication, particularly in patients with underlying psychiatric comorbidity[1]
- Traumatic injury
  - Increased risk of traumatic injury is associated with acute ethanol intoxication[8]
  - Clinical course of traumatic injury associated with ethanol use may be worse, with increased risk for intubation, duration of hospitalization, and mortality[8]
- Violent crime
  - Binge drinking is associated with increased risk of homicide, assault, robbery, and sexual offenses[8]
- Death
  - Lethal dose is variable
    - Death attributable to acute intoxication generally occurs with concentrations exceeding 500 mg/dL[8]
    - Death attributable to acute intoxication in nontolerant or ethanol-naive patients may occur at lower concentrations (eg, 300-500 mg/dL)[8]
    - Fatal complications may occur at much lower blood ethanol concentrations in children (less than 50 mg/dL)[6]
  - Cause of death is usually respiratory arrest with or without aspiration

PROGNOSIS

- General prognosis of uncomplicated acute ethanol toxicity is favorable with appropriate supportive care

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SCREENING AND PREVENTION

SCREENING

PREVENTION

- Prevent accidental ingestion in children by educating caregivers of risk and making substances inaccessible (eg, ethanol-containing mouthwash, cosmetics, cleaning products, beverages)[2]

SYNOPSIS

KEY POINTS

- Acute ethanol toxicity results from ingesting ethanol faster than it can be metabolized by the liver and eliminated, leading to accumulation of ethanol and its metabolites in the blood
- Ethanol intoxication presents with variable manifestations progressing from mild (eg, altered sensorium, ataxia, incoordination, nystagmus) to severe (eg, stupor, respiratory depression, coma) with increasing blood ethanol concentrations
- Children are at particularly high risk for adverse effects of ethanol (eg, hypoglycemia, hypothermia, coma) despite relatively small amount of ethanol ingested
- Acute toxicity is diagnosed by clinical presentation and *DSM-5* criteria
- Ancillary studies may be required depending on individual presentation (eg, glucose, electrolytes, blood or breath ethanol levels)
- Additional considerations at time of presentation include exclusion of occult trauma and alternative diagnosis
- Treatment largely involves symptomatic care; no antidote is available for ethanol intoxication; replace thiamine when indicated
- Conditions associated with acute ethanol toxicity that may require treatment include hypoglycemia, dehydration, vomiting, electrolyte abnormalities (eg, hyponatremia, hypomagnesemia), seizures, and agitation
- Potential complications are numerous and include aspiration, gastritis, pancreatitis, cardiac arrhythmias, increased risk of suicide and violent crime, and death
- General prognosis of uncomplicated acute ethanol toxicity is favorable with appropriate supportive care

URGENT ACTION

- Standard airway protection and respiratory support may be required for obtunded patients or patients with respiratory depression
- Treat hypotension secondary to volume depletion and dehydration in standard fashion beginning with isotonic IV fluid bolus
- Hypoglycemia requires immediate correction with dextrose bolus followed by infusion and frequent monitoring
- Seizures are often caused by hypoglycemia; correct hypoglycemia and treat continued seizure activity in standard fashion; seizure activity without hypoglycemia suggests presence of intracranial pathology (eg, hemorrhage) or significant electrolyte abnormality (eg, hyponatremia)
- Hypothermia requires immediate external warming measures (eg, warm blankets, external warming system)
- First line treatment for significant agitation and aggression is a typical antipsychotic (eg, haloperidol)

PITFALLS

- Diagnosis of acute ethanol intoxication may lead some clinicians to disregard search for additional severe disease and occult injury
  - Evaluate and monitor for occult trauma, potential alcohol-related disease, and non–alcohol-related conditions in patients diagnosed with acute ethanol intoxication[6]
  - Avoid temptation to rapidly discharge unruly patients and to minimize issues in pleasantly intoxicated patients[8]
- Young children are prone to significant hypoglycemia and other serious effects (eg, coma, hypothermia) with exposure to relatively small amounts of ethanol
  - Maintain care to aggressively monitor for and treat life-threatening ethanol-related effects in young children
- Maintain awareness of limitations of blood ethanol concentration measurement; the concentration values do not necessarily correlate with clinical presentation, they lack predictive ability regarding clinical severity and outcome, and they often do not affect treatment decisions

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