As eloquently stated by Paracelsus in the 16th century, “all substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.”

**Epidemiology**

The disastrous effects and widespread incidence of alcoholism are well known to the emergency physician. Almost all societies that consume alcohol show related health and social problems. Motor vehicle collisions, drowning, suicides, homicides, divorce, violent crime, child abuse, unemployment, and disruption of the family are often either directly or indirectly associated with excessive alcohol consumption. The tragic effects of alcohol not only affect the individual drinker but also have far-reaching implications for the family, community, and workplace. In the United States, an estimated 7.6 million visits to the emergency department (ED) a year are related to alcohol, accounting for 7.9% of all ED visits. Table 185-1 lists the causes of death related to alcohol abuse.

Alcohol is the most common recreational drug taken by Americans, and per capita consumption is increasing. An estimated 18 million alcoholics live in the United States; with more than 85,000 alcohol-related deaths each year, resulting in 2.3 million years of potential life lost, alcohol is the third leading cause of preventable death in the United States. Alcoholism permeates all levels of society and is a preventable cause of morbidity and mortality, with a cost to the nation estimated to be greater than $185 billion annually.

The alcohol-use disorders consist of alcohol dependence, alcohol abuse, and dependence or harmful use. These disorders are common in all developed countries and are more prevalent in men than in women, with lower but still substantial rates in developing countries. However, most people with alcohol-use disorders are difficult to identify because they are likely to have jobs and families and to present with general complaints, such as malaise, insomnia, anxiety, sadness, or a range of medical problems.

**Diagnosis**

Alcohol dependence is associated with major physiologic consequences and life impairment. Dependence can be identified as repetitive problems, affecting three or more areas of life, and about 80% of people who are diagnosed with dependence at any point still have alcohol-related problems when they are assessed a year or more later. Dependence criteria are reliable across different ages, sexes, and most cultural groups. Alcohol abuse is defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as one or more problems with functioning in a 12-month period in a person without dependence: failure in obligations; alcohol use in hazardous situations; recurrent legal problems; or continued use despite social or interpersonal problems.

**Alcohol Screening Questionnaires**

Detection of risky drinking behaviors can be through clinical history or the administration of short alcohol screening tools in the ED setting, such as the Alcohol Use Disorders Identification Test (AUDIT), Fast Alcohol Screening Test (FAST), and CAGE questionnaires. The objectives of these screening tools vary; the AUDIT and FAST are focused on detection of recent hazardous or harmful alcohol consumption and associated problems, whereas the CAGE is designed to detect lifetime alcohol dependence.

**The AUDIT-C Screening Questionnaire**

1. How often do you have a drink containing alcohol?
   - Never (0 points), monthly or less (1 point), two to four times a month (2 points), two or three times a week (3 points), four or more times a week (4 points)
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   - 1 or 2 (0 points), 3 or 4 (1 point), 5 or 6 (2 points), 7 to 9 (3 points), 10 or more (4 points)
3. How often do you have six or more drinks on one occasion?
   - Never (0 points), less than monthly (1 point), monthly (2 points), weekly (3 points), daily or almost daily (4 points)

Scoring: The sum of scores for the three questions results in an AUDIT-C score of 0 to 12 points. The AUDIT-C screening thresholds are ≥24 points for men (sensitivity 86%, specificity 89%) and ≥3 points for women (sensitivity 73%, specificity 91%).

A positive answer to the question Have you ever had a drinking problem? plus evidence of alcohol consumption in the previous 24 hours provides greater than 90% sensitivity and specificity as a screening tool for identification of alcoholism.

Blood tests can be useful if the history is in doubt and can also help patients recognize that alcohol has adversely affected their health. One such marker is γ-glutamyltransferase, an enzyme important in amino acid transport. Results of at least 35 units/L indicate the probability of heavy drinking. A second test is for carbohydrate-deficient transferrin, which measures a change in the structure of a proportion of transferrin that is likely to occur with heavy drinking during a long period; a result of 20 units/L or more indicates heavy drinking. Tests of liver function that measure aspartate transaminase (AST) and alanine transaminase (ALT) can identify heavy drinking and alcohol-use disorders with...
sensitivities of 25 to 45% and specificities as high as 90%. A ratio of AST to ALT higher than 2, especially if concentrations of these enzymes do not exceed 400 units/L, suggests alcoholic hepatitis. Although many newer biomarkers are not yet available, these newer markers (acetaldehyde adducts) rely on protein modifications by acetaldehyde and play an important role in the pathogenesis of tissue damage in alcoholics (Tables 185-2 and 185-3).

### Pathophysiology

#### Causes and Origins

About 40 to 60% of the risk of alcohol-use disorders is explained by genes and the rest through gene-environment associations. The environment includes the availability of alcohol, attitudes toward drinking and drunkenness, peer pressures, levels of stress and related coping strategies, models of drinking, and laws and regulatory frameworks.

First, variations (polymorphisms) in genes for enzymes that metabolize alcohol are generally associated with a lower risk of alcohol-use disorders because they increase sensitivity to alcohol. At least one variant of aldehyde dehydrogenase (the ALDH2*2 allele) produces an aversive response to alcohol. Second, gene forms associated with impulsivity, disinhibition, and sensation seeking contribute to vulnerability to both drug-use and alcohol-use disorders, perhaps through impaired judgment and difficulty in learning from mistakes that could reduce control of alcohol intake. Relevant polymorphisms include variations in receptors for γ-aminobutyric acid (e.g., GABRA2), acetylcholine (e.g., CHRM2), and dopamine (e.g., DRD2). Third, people who have low responsiveness (or low sensitivity) to alcohol are more likely to drink more on each occasion to obtain the desired effect, which increases their risk of alcohol-use disorders but not of other drug-related disorders. Additional genetic mechanisms might regulate dopamine-reward systems.

#### Definition and Natural History

A precise definition of alcoholism is difficult. A proposed definition encompassing the features of alcoholism is “a primary chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.” The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with and use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Each of these symptoms may be periodic or continuous. A precise definition of alcoholism is difficult. A proposed definition encompassing the features of alcoholism is “a primary chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.” The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with and use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Each of these symptoms may be periodic or continuous.

### Table 185-1 Causes of Death Related to Alcohol Abuse

<table>
<thead>
<tr>
<th>MARKER</th>
<th>ABBREVIATION</th>
<th>HALF-LIFE/ELIMINATION RATE</th>
<th>CLINICAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood ethanol</td>
<td>EtOH</td>
<td>1 g/1 h/10 kg</td>
<td>Levels exceeding 1.5% without evidence of intoxication or 3% at any time indicate ethanol tolerance typically found in alcohol abusers and alcohol-dependent patients. Suitable for emergency clinics</td>
</tr>
<tr>
<td>γ-Glutamyltransferase</td>
<td>GGT</td>
<td>2-3 weeks</td>
<td>A sensitive and inexpensive marker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity decreased by obesity, diabetes, nonalcoholic liver diseases, pancreatitis, hyperlipidemia, cardiac insufficiency, severe trauma, medications (barbiturates, drugs for epilepsy, anticoagulants), nephrotic syndrome, renal rejection</td>
</tr>
<tr>
<td>Mean corpuscular volume of</td>
<td>MCV</td>
<td>2-4 months</td>
<td>More sensitive in women</td>
</tr>
<tr>
<td>erythrocytes</td>
<td></td>
<td></td>
<td>Specificity decreased by vitamin B12 or folic acid deficiency, liver diseases, hematologic diseases, hypothyroidism, reticulocytosis, smoking</td>
</tr>
<tr>
<td>Carbohydrate-deficient</td>
<td>CDT</td>
<td>2-3 weeks</td>
<td>Most specific of the currently available methods</td>
</tr>
<tr>
<td>transferrin (desialotransferrin)</td>
<td></td>
<td></td>
<td>Specificity decreased by genetic variants of transferrin on rare occasions</td>
</tr>
<tr>
<td>GGT-CDT combination</td>
<td>GGT-CDT (γ-CDT)</td>
<td>2-3 weeks</td>
<td>A mathematically formulated combination that is easy to manage in hospital laboratories</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improves sensitivity without a loss of specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Good correlation with the amount of recent ethanol intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suitable for routine use</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>AST, ALT</td>
<td>2-3 weeks</td>
<td>AST/ALT ratio above 2 suggests alcoholic etiology in liver disease patients</td>
</tr>
</tbody>
</table>


Men: more than 14 drinks per week or more than 4 drinks per occasion
Women: more than 7 drinks per week or more than 3 drinks per occasion
Age older than 65 years: more than 7 drinks per week or more than 1 drink per occasion

Harmful drinkers present with negative consequences related to alcohol.

The natural history of alcoholism is variable, and it may appear in any patient despite age or social status. The age at onset of alcoholism continues to decrease. Up to 6% of high school seniors drink daily, and it is not unusual to see children younger than 16 years who have already graduated from an alcohol detoxification program. Many individuals also begin drinking heavily after the age of 60 years.

The DSM-IV has two categories for substance disorders that include alcohol abuse: (1) substance abuse and (2) substance dependence. The chronic substance abuse of alcohol eventually leads to acquired tolerance, a condition in which larger and larger doses of alcohol are required for the same effect.

### Table 185-3 Emerging Biomarkers in Alcoholism

<table>
<thead>
<tr>
<th>MARKER</th>
<th>ABBREVIATION</th>
<th>HALF-LIFE/ELIMINATION RATE</th>
<th>CLINICAL CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde adducts</td>
<td>AA</td>
<td>Depends on carrier protein</td>
<td>Present in circulation and tissues of alcoholics. Antigen for autoimmune responses. Anti-adduct IgAs specific for alcohol abusers.</td>
</tr>
<tr>
<td>5-Hydroxytryptophol</td>
<td>5-HTOL</td>
<td>14-15 hours</td>
<td>Measurements from urine. Sensitive indicator of relapses. 5-HTOL ratio to 5-hydroxyindole-3-acetic acid improves specificity.</td>
</tr>
<tr>
<td>Ethyl glucuronide</td>
<td>EtG</td>
<td>3-5 days</td>
<td>Measurements from urine.</td>
</tr>
<tr>
<td>Phosphatidylethanol</td>
<td>PEth</td>
<td>2 weeks</td>
<td>A specific metabolite of ethanol. Sensitive to sample storage.</td>
</tr>
<tr>
<td>Sialic acid</td>
<td>SA</td>
<td>2-5 weeks</td>
<td>Sensitive for alcohol abuse but lacks specificity. May help differentiate between alcohol abuse and secondary effects of liver disease.</td>
</tr>
</tbody>
</table>


PRINCIPLES OF DISEASE: METABOLISM OF ALCOHOL

Ethanol is rapidly absorbed from the stomach and small intestine. It is distributed uniformly to all organ systems, including the placenta. Although 2 to 10% of alcohol is excreted through the lungs, urine, and sweat, the majority is metabolized to acetaldehyde, primarily by alcohol dehydrogenase (ADH). The oxidation of alcohol is a complex process involving three enzyme systems, all contained in the hepatocyte. The class I ADH isoenzymes, ADH1A, ADH1B, and ADH1C, oxidize ethanol, but ADH1B and ADH1C have polymorphic properties with distinct kinetic properties. Acetaldehyde is then quickly converted to carbon dioxide and water, primarily through aldehyde dehydrogenase (ALDH). The common forms of ADH decrease the alcohol concentration in blood by about 4.5 mmol/L ethanol per hour (the equivalent of about one drink per hour).

```
Ethanol  →  Alcohohydrogenase  →  Acetaldehyde  →  Acetyl coenzyme A
          NAD+  →  NADH  →  NAD+  →  CO2 + H2O
```

At least two variations of ADH genes (ADH1B*2 and ADH1C*1) produce a slightly more rapid breakdown of alcohol and therefore potentially faster production of acetaldehyde, which is rapidly metabolized by ALDH2. However, about 40% of Asian people (Japanese, Chinese, and Koreans) have an inactive ALDH2 mutation that results in much higher acetaldehyde levels after drinking than normal. About 10% of people who are homozygous for this gene form cannot drink alcohol without becoming sick and have almost no risk of alcohol-use disorders, whereas those who are heterozygous have a relatively low rate of alcohol-use disorders.

An alternative pathway, the microsomal ethanol-oxidizing system (MEOS), is induced by chronic alcohol exposure. The primary component of the MEOS is the molecule cytochrome P450, which exists in several variants. The variant most important for alcohol metabolism is cytochrome P450 2E1 (CYP2E1). Many effects of alcoholism are produced by the toxic byproducts (hydrogen, acetaldehyde), the acceleration of metabolism of other drugs, and activation of hepatotoxic compounds by these metabolic pathways.

Although the liver is the major site of ethanol metabolism, other tissues contribute to its metabolism. ADH is found in the gastric mucosa, but the gastric metabolism of alcohol is decreased in women and those of Asian descent. This increased bioavailability of ethanol or decreased first-pass metabolism may explain the greater vulnerability of women to acute and chronic complications of alcohol.

Alcohol elimination has two phase curves. The alcohol elimination rate approximates zero-order kinetics (constant rate) for lower ethanol levels and first-order kinetics (amount of drug removed over time is proportional to the concentration of the drug) for higher levels, especially in chronic alcoholics; most likely, through induction of the MEOS pathway, the elimination rate is increased at higher blood levels.

The absorption and elimination rates of alcohol vary by individual and depend on many factors: diet, gender, body weight and habits, speed of consumption, gastric motility, presence of food in the stomach, smoking history, age, whether the person is a chronic alcohol consumer with enzyme induction and high-activity MEOS, advanced cirrhosis, presence of ascites, and state of nourishment. There is enormous variation among patients in the rate of disappearance of ethanol from the blood, ranging from 9 to 36 mg/dL per hour in published data. Although the clearance rate may be as high as 36 mg/dL per hour in some chronic drinkers, 20 mg/dL per hour is a reasonable rate to assume in a typical intoxicated ED patient. This holds true for adults, adolescents, and children.

Physiologic effects vary directly with the blood alcohol level (Table 185-4). Diminished fine motor control and impaired judgment appear with alcohol concentrations as low as 20 mg/dL.
quantitative testing. More than 50% of the adult population is documented before the empirical administration of glucose. With consideration of a person cannot be accurately determined without administration of IV for hypoglycemia, and naloxone (0.8 mg) to treat Wernicke-Korsakoff syndrome, glucose (dextrose, 25 to 50 g IV) produces a dramatic response in alcohol-induced hypoglycemic patients. Unlike hypoglycemia of other causes, alcohol-induced hypoglycemia may be unresponsive to glucagon because of depleted liver glycogen stores. Although Wernicke's encephalopathy is a medical emergency, alcohol-induced hypoglycemia is a much more common condition with serious and permanent morbidity if it is left untreated. Therefore, thiamine can be given in a timely fashion, but glucose therapy should not be delayed. Intoxicated patients require evaluation and treatment in the ED regardless of their obstreperousness. Inappropriate discharge and failure to diagnose are two common areas of liability in treatment of the alcohol-dependent patient. The theoretic liability for detention by reasonable restraint is less than the potential liability for injury sustained by the alcohol-dependent patient or an innocent bystander after premature discharge. Discharge can be considered when a patient is clinically sober and able to dress, walk, and function independently as judged and well documented by the treating clinician. Under ideal circumstances, another concerned, sober adult is available and willing to take responsibility for and remain with the patient for the next 24 to 48 hours.

### ALCOHOL WITHDRAWAL SYNDROME

#### Principles of Disease

The neurophysiology of alcohol withdrawal is complex and not fully understood. Chronic alcohol consumption has a depressant effect on the central nervous system (CNS). The hallmark of alcohol withdrawal is CNS excitation with increased cerebrospinal fluid, plasma, and urinary catecholamine levels. Chronic alcohol consumption affects central adrenergic alpha receptors, glutamate, central adrenergic beta receptors, the inhibitory neurotransmitter \( \gamma \)-aminobutyric acid (GABA), and dopamine turnover.

#### Differential Considerations

Alcohol withdrawal syndrome can initially be confused with acute schizophrenia, encephalitis, drug-induced psychosis, thyrotoxicosis, anticholinergic poisoning, and withdrawal from other drugs of the sedative-hypnotic type. It may be difficult to differentiate between alcohol withdrawal and alcohol-induced hypoglycemia.

Signs of alcohol withdrawal usually begin 6 to 24 hours after a decrease in the patient's usual intake of alcohol. If patients manifest withdrawal 3 to 4 days or more after their last drink, drugs with a longer half-life should be considered. The barbiturate and benzodiazepine withdrawal syndromes usually progress more slowly, with a higher frequency of seizures later (7 days versus 2 days), and status epilepticus is more common than with alcohol withdrawal.

#### Clinical Features

Isbell's classic study in 1955 confirmed the relationship between alcohol and the withdrawal syndrome. He documented that the severity of signs and symptoms depends on both the dose and the duration of ethanol consumption. The withdrawal syndrome may occur any time after the blood alcohol level starts to fall. Therefore, only a reduction, not the abrupt cessation, of ethanol intake may result in withdrawal.

Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after cessation of or significant decrease in alcohol intake. It is characterized by mild autonomic hyperactivity: nausea, anorexia, coarse tremor, tachycardia, hypertension,

<table>
<thead>
<tr>
<th>BLOOD ALCOHOL CONCENTRATION (mg/dL)</th>
<th>EFFECTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-50</td>
<td>Diminished fine motor control</td>
</tr>
<tr>
<td>50-100</td>
<td>Impaired judgment; impaired coordination</td>
</tr>
<tr>
<td>100-150</td>
<td>Difficulty with gait and balance</td>
</tr>
<tr>
<td>150-250</td>
<td>Lethargy; difficulty sitting upright without assistance</td>
</tr>
<tr>
<td>300</td>
<td>Coma in the novice drinker</td>
</tr>
<tr>
<td>400</td>
<td>Respiratory depression</td>
</tr>
</tbody>
</table>

*These effects are for the occasional drinker. Chronic drinkers can function at much higher alcohol concentrations because of tolerance. On the other hand, patients may become comatose with low levels of alcohol in mixed alcohol-drug overdose.

(0.02 mg%), but wide individual variability exists. Chronic alcoholics can exhibit impressive tolerance. The blood alcohol concentration of a person cannot be accurately determined without quantitative testing. More than 50% of the adult population is obviously intoxicated with a level of 150 mg/dL (0.15 mg%). As the ethanol level rises, the patient’s level of consciousness declines, eventually ending in coma. Death is caused by aspiration or respiratory depression.

Alcohol through passive diffusion will be present anywhere there is water in the body. Hence, expired breath alcohol or saliva can be used to obtain a reliable approximation of blood alcohol concentration in a cooperative patient. This value can be used as a rapid screen for alcohol intoxication.

**DIFFERENTIAL CONSIDERATIONS**

Acute alcohol intoxication is a diagnosis of exclusion. Before it is assumed that a patient’s behavior is caused only by alcohol, other conditions should be considered. Hypoglycemia, hypoxia, carbon dioxide narcosis, mixed alcohol-drug overdose, ethylene glycol poisoning, isoopropranol or methanol poisoning, hepatic encephalopathy, psychosis, severe vertigo, postictal state, and psychomotor seizures can be manifested in a manner similar to ethanol intoxication. The possibility of occult head trauma and the presence of associated metabolic disorders should be considered after alcohol intoxication has been established. Shock from gastrointestinal bleeding or sepsis, hypothermia, hyperthermia, and hepatic encephalopathy are all possible. These potentially catastrophic diagnoses are usually detected by a thorough history and physical examination, a blood alcohol level (as coma is rare in chronically intoxicated patients with blood alcohol levels below 200 mg/dL), and close observation (an intoxicated patient’s level of consciousness should constantly improve over time). Adequate history from paramedics and family, repeated physical examinations by the same clinician, and diagnostic adjuncts can help resolve this dilemma.

**MANAGEMENT**

Comatose or stuporous patients need to have airway and ventilation evaluated and managed with endotracheal intubation as necessary. Thiamine (100 mg intravenously [IV]) to prevent or to treat Wernicke-Korsakoff syndrome, glucose (dextrose, 25 to 50 g IV) for hypoglycemia, and naloxone (0.8 mg IV) for possible opioid ingestion should be considered in comatose patients. As magnesium is a necessary cofactor for thiamine metabolism, consider magnesium 2 g IV. When possible, hypoglycemia should be documented before the empirical administration of glucose. With the airway maintained and respirations supported, the patient’s liver eventually metabolizes the alcohol, and most patients recover. Glucose (dextrose, 25 g IV) produces a dramatic response in alcohol-induced hypoglycemic patients. Unlike hypoglycemia of other causes, alcohol-induced hypoglycemia may be unresponsive to glucagon because of depleted liver glycogen stores. Although Wernicke’s encephalopathy is a medical emergency, alcohol-induced hypoglycemia is a much more common condition with serious and permanent morbidity if it is left untreated. Therefore, thiamine can be given in a timely fashion, but glucose therapy should not be delayed. Intoxicated patients require evaluation and treatment in the ED regardless of their obstreperousness. Inappropriate discharge and failure to diagnose are two common areas of liability in treatment of the alcohol-dependent patient. The theoretic liability for detention by reasonable restraint is less than the potential liability for injury sustained by the alcohol-dependent patient or an innocent bystander after premature discharge. Discharge can be considered when a patient is clinically sober and able to dress, walk, and function independently as judged and well documented by the treating clinician. Under ideal circumstances, another concerned, sober adult is available and willing to take responsibility for and remain with the patient for the next 24 to 48 hours.
hyper-reflexia, sleep disturbances (e.g., insomnia, vivid dreams),
and anxiety.17

Major alcohol withdrawal occurs after more than 24 hours and
usually peaks at 50 hours but occasionally takes up to 5 days to be
manifested after the decline or termination of drinking. The syn-
drome is characterized by pronounced anxiety, insomnia, irritabil-
ity, tremor, anorexia, tachycardia, hyper-reflexia, hypertension,
fever, decreased seizure threshold, auditory and more commonly
visual hallucinations, and finally delirium.18

Delirium tremens is a life-threatening manifestation of alcohol
withdrawal and consists of gross tremor, frightening visual halluci-
inations, profound confusion, agitation, and a hyperadrenergic
syndrome characterized by temperature above 101°F, blood pres-
sure higher than 140/90 mm Hg, and tachycardia. It seldom
appears before the third post-abstinence day. Only 5% of patients
hospitalized for alcohol withdrawal have delirium tremens.

Management

Family, friends, bystanders, or paramedics often give more reliable
historical data than the patient does. Accurate vital signs are essen-
tial. This may require a rectal temperature. Hyperthermia, hypo-
thermia, tachypnea, or tachycardia may suggest serious disorders
that often accompany the alcohol-dependent patient. These disor-
ders should be considered during this first assessment.

A rapid, thorough examination should be performed with
attention to the level of consciousness, signs of hepatic failure, or
cogulopathy. Signs of trauma are sought, such as subcutaneous
emphysema, ecchymosis, subconjunctival hemorrhage, hemotym-
panum, or Battle’s sign, and palpation is done for occult injuries.
The neurologic examination should search for focal findings,
including central facial nerve palsy, hemiparesis, and asymmetry
of pupillary response.

The alcohol withdrawal syndrome should be promptly recog-
nized and treated to provide relief from anxiety and hallucinations;
to halt progression to major withdrawal and withdrawal seizures;
to allow detection of a treatable primary psychiatric illness; to
prepare the patient for long-term alcohol abstinence with the
lowest risk of new drug dependence; and to calm the patient and
allow adequate examination for the detection of medical illnesses
that typically accompany alcoholism, such as gastritis, dehydration,
pancreatitis, pneumonia, electrolyte disorders, and hepatitis.

In combination with appropriate chemical sedation, detention
by reasonable restraint may be an option to prevent potential
injury that patients may inflict on themselves or the hospital staff.
These appropriate measures need to be instituted, and decision-
challenged patients should not be permitted to sign an “against
medical advice” form and be discharged.

Patients suffering from alcohol withdrawal should receive phar-
macologic intervention along with supportive care. The ideal drug
for alcohol withdrawal would have a rapid onset, wide margin of
safety, metabolism not dependent on liver function, and limited
abuse potential. Although no one drug class fits all these require-
ments, benzodiazepines are clearly the mainstay of treatment.

Benodiazepines. The benzodiazepines have superior anticon-
vulsant activity, have the least respiratory and cardiac depressive
effect of all the CNS depressants, and can be given parenterally in
the uncooperative patient. By interacting with receptors linked
to the GABA-associated chloride ion channel, benzodiazepines
substitute for the withdrawal of the GABA-potentiating effect
of alcohol and abate withdrawal signs and symptoms.19 Numerous
benzodiazepines have been studied, but there is no evidence of
clear superiority of any one benzodiazepine.

Lorazepam has good bioavailability with oral, intramuscular,
and intravenous routes. It is rapidly and completely absorbed from
intramuscular sites in agitated patients with no intravenous access.
Lorazepam’s half-life is intermediate (7-14 hours), and it reaches
a steady state in 36 to 48 hours without active metabolites. Exces-
sive sedation, confusion, and ataxia are potential complications of
all benzodiazepines with prolonged half-lives. Lorazepam is
metabolized (conjugated) in the liver, yielding inactive products.
Although the half-life of lorazepam increases in patients with cir-
rhosis or liver failure, it is much less than the increase with chlor-
diazepoxide. Lorazepam’s elimination is only minimally altered in
patients with renal failure and in the elderly. Lorazepam may be
given intravenously in a dose of 1 to 4 mg, depending on the severity
of the withdrawal. Dosing can be repeated at 5- to
15-minute intervals for patients in severe withdrawal. Although it
is not ideal, an intramuscular dose of 1 to 4 mg can be used every
30 to 60 minutes until the patient is calm and then every hour as
needed for light somnolence. The oral schedule for moderate
withdrawal is 6 mg/day in three divided doses, tapering the
amount by 1 to 2 mg/day during 4 to 6 days.

As one dosing regimen, diazepam, 5 mg IV every 5 to 10 minutes
(2.5 mg/min), can be given in major withdrawal until the patient
is calm. The dose can be repeated in 5 to 10 minutes. If the second
dose of 5 mg is not working, consider 10 mg for the third and
fourth doses every 5 to 10 minutes. If this is not effective, consider
20 mg for the fifth and subsequent dose until adequate sedation is
obtained.20,21

Butyrophenones. Haloperidol, a dopamine antagonist, can be
considered in patients with major alcohol withdrawal or delirium
tremens not responding to intravenous benzodiazepines. Halo-
peridol has little effect on myocardial function or respiratory
drive, and its safety and efficacy by the intravenous, intramuscular,
or oral route in the ED have been established. Haloperidol has no
anticonvulsant properties; however, extrapyramidal effects may be
seen. Caution should be used in patients who may be susceptible
to a prolonged QTc. Droperidol has effects similar to those of
haloperidol. Despite the 2001 Food and Drug Administration
black box warning for QTc prolongation and torsades de pointes
after droperidol use, droperidol remains a safe and effective treat-
ment for agitated patients.22

Emergency Department and
Outpatient Approaches

Outpatient treatment consists of lorazepam, 1 to 2 mg three times
a day in a tapering dose for 3 to 6 days; chlordiazepoxide, 25 to
100 mg three times a day, in a tapering dose for 3 to 6 days; or
diazepam, 30 mg once a day tapered during 5 days, depending on
the severity of symptoms. Adequate diet, abstinence, and participa-
tion in a rehabilitation program in the community are also desir-
able. Any patient requiring 300 mg of chlordiazepoxide or 60 mg
of diazepam per day to control withdrawal should be considered
for admission. Patients with major alcohol withdrawal (disorienta-
tion, hallucinations, diaphoresis, or fever) are admitted.

Adjuective Therapy

Patients being treated for major alcohol withdrawal may be given
thiamine (100 mg IV) and magnesium (2 g IV). Although mag-
nesium sulfate does not decrease the severity of withdrawal symp-
toms, the incidence of delirium, or seizures, it carries no significant
risk (with adequate renal function).

If volume depletion is present, it can be corrected with normal
saline. Reversal of electrolyte and metabolic disorders (hypomag-
nesemia, hypophosphatemia, hypokalemia, and acidosis) benefits
the patient, but it does not abate the withdrawal syndrome.

ALCOHOL-RELATED SEIZURES

Among the many medical problems related to alcohol abuse, the
differential diagnosis and management of seizures remain among
the most challenging and controversial (Box 185-1). Patients presenting to the ED with seizures should be questioned about alcohol intake. Of seizure patients presenting to an ED, 20 to 40% will have their seizures related to alcohol use or abuse.\textsuperscript{23} Alcohol is a causative factor in 11 to 24% of patients with status epilepticus.\textsuperscript{24,25} In states where alcohol sales are restricted on Sundays, EDs can be reduced to 3% with lorazepam administration after the generalized tonic-clonic seizures. Sixty percent experienced multiple seizures after the cessation of drinking. Ninety percent had one to six episodes.\textsuperscript{26} The primary consideration in the initial care of seizure patients who use alcohol is the recognition of treatable, life-threatening causes. These causes include but are not limited to CNS infection, metabolic disorders, and intracranial hemorrhage. Alcohol may act in one of several ways to produce seizures in patients with or without underlying foci: by its partial or absolute withdrawal after a period of chronic intake, by an acute alcohol-related metabolic disorder (e.g., hypoglycemia, hyponatremia), by creation of a situation leading to cerebral trauma, by precipitation of seizures in patients with idiopathic or post-traumatic epilepsy, or by lowering of the seizure threshold in patients with prior existing intracerebral disease states. Moreover, alcoholics are more susceptible to other disorders associated with seizures, including neurosyphilis, acquired immunodeficiency syndrome (AIDS), brain abscess, and meningitis.\textsuperscript{27-29}

**Alcohol Withdrawal Seizures**

Descriptions of alcohol withdrawal seizures are based on data collected by Victor and Brausch.\textsuperscript{30} Seizures occurred 6 to 48 hours after the cessation of drinking. Ninety percent had one to six generalized tonic-clonic seizures. Sixty percent experienced multiple seizures within a 6-hour period. However, seizure recurrence can be reduced to 3% with lorazepam administration after the initial seizure.\textsuperscript{31} The incidence of partial seizures, common with post-traumatic epilepsy, is increased in alcohol withdrawal. The term *alcohol withdrawal seizure* is reserved for seizures with the characteristics described by Victor and Brausch.\textsuperscript{30} The term *alcohol-related seizure* is used to refer to all seizures in the aggregate associated with alcohol use, including this subset of alcohol withdrawal seizure.

**Patients Presenting with Normal Findings on Neurologic Examination**

**New-Onset Alcohol-Related Seizures**

Patients with new-onset alcohol-related seizure should be thoroughly evaluated. This includes alcoholics who claim to have had seizures but for whom no documentation or an appropriate work-up is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities should be considered. Laboratory and radiographic testing to include electrolyte values and blood urea nitrogen, creatinine, glucose, and anticonvulsant levels and brain computed tomography (CT) scan may be necessary. Of 259 patients presenting with their first alcohol-related seizure, clinical management was changed in 3.9% on the basis of head CT results.\textsuperscript{32}

If the initial physical examination findings, imaging studies, and laboratory test results are within normal limits, patients who remain seizure free and symptom free with no sign of withdrawal after 4 to 6 hours of observation may be discharged. It may be unclear whether the patient has had a pure alcohol withdrawal seizure or a new-onset seizure disorder in the setting of alcohol ingestion. Long-term treatment with antiepileptic drugs is not useful in unprovoked new-onset seizures that have resolved or when a clear relation to alcohol consumption can be identified.

Optimal outpatient treatment includes follow-up and referral to a detoxification or rehabilitation program. Ideally, the help of a concerned family member or friend who is not a drinking partner and can remain with the patient for at least 1 or 2 days is helpful.

**Seizures in the Alert Patient with a History of Seizures during Prior Withdrawal**

The risk of seizure increases significantly in alcoholic patients with manifestations of alcohol withdrawal who relate a history of alcohol withdrawal seizure.\textsuperscript{33,34} Detoxification with benzodiazepines reduces alcohol withdrawal seizure and should be initiated early because most seizures occur within the first 24 hours after alcohol withdrawal. An initial dose of 2 mg of lorazepam or 5 mg of diazepam can be given intravenously. These doses frequently need to be repeated.\textsuperscript{35} The patient should be observed for 4 to 6 hours before discharge is considered. The prescription of benzodiazepines or antiepileptic drugs on discharge carries its own hazards. Benzodiazepines (other than a short 3- to 6-day tapering dose for withdrawal) may increase the potential risk of addiction. In a noncompliant patient, antiepileptic drugs, such as phenytoin, may paradoxically increase the number of seizures. The poorly compliant alcoholic patient may do better without outpatient anticonvulsants for a concurrent seizure disorder.\textsuperscript{33} The ideal disposition is referral to a detoxification or rehabilitation unit.

**Patients with an Abnormal Neurologic Presentation**

**New-Onset Partial Seizures**

Partial seizures account for 24 to 51% of alcohol-related seizures.\textsuperscript{36} Conversely, studies have shown that 17 to 21% of patients with partial alcohol-related seizure have structural lesions: hematomas, tumors, vascular abnormalities, or stroke.\textsuperscript{37} These primary causes of partial alcohol-related seizure, such as prior head trauma, may be easily missed in the history taking. As a result, an emergent CT scan is indicated to evaluate new-onset partial seizures. The patient with a history of a focal alcohol-related seizure who has been previously evaluated does not require an emergency CT scan, provided a return to baseline occurs promptly. A patient presenting with a focal alcohol-related seizure with subsequent normal neuroimaging findings can be managed with supportive care, observation for 4 to 6 hours, and a benzodiazepine for withdrawal signs or symptoms. Appropriate follow-up should be arranged.

**Obtundation**

The obtunded or stuporous alcohol-dependent patient with a history of seizure activity poses a diagnostic challenge. The patient's decreased level of consciousness may be the result of a postictal state, occult head trauma, unrecognized metabolic

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**Box 185-1**

**Differential Diagnosis of Alcohol-Related Seizures**

- Withdrawal (alcohol or drugs)
- Exacerbation of idiopathic or post-traumatic seizures
- Acute intoxication (amphetamine, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium)
- Metabolic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure)
- Infectious (meningitis, encephalitis, brain abscess)
- Trauma (intracranial hemorrhage)
- Cerebrovascular accident
- Sleep deprivation
- Noncompliance with anticonvulsants
disorder, or other poisoning. The first diagnostic task is quickly to determine the possibility of hypoglycemia (diagnosed and reversed at the bedside in minutes) and to evaluate for other metabolic and toxic causes of altered mental status. Patients with an acute alteration in mental status should undergo a head CT scan if they are not demonstrating expected and obvious improvement.

Patients Taking Phenytoin-Anticonvulsant

Phenytoin has no significant benefit over placebo in prevention of recurrence of uncomplicated (e.g., no old subdural) alcohol withdrawal seizure. Considering the risks of phenytoin and no demonstrated benefit in the setting of alcohol withdrawal seizure, it is not indicated for the treatment of alcohol withdrawal seizure. The sudden withdrawal of phenytoin may potentiate the convulsive effects of alcohol withdrawal.23,38

A patient currently taking antiepileptic drugs for an antecedent seizure disorder who presents with a seizure while intoxicated falls into a different category. Such an episode could be an isolated event in a usually compliant patient without a history of chronic alcohol abuse. In this patient, a seizure in the setting of a subtherapeutic antiepileptic drug level may represent the consequences of noncompliance with antiepileptic medication or sleep deprivation versus alcohol withdrawal seizure.33

OTHER CLINICAL FEATURES AND MANAGEMENT

Cardiovascular Effects

Acute and chronic ethanol consumption can affect the mechanical function of the heart, produce dysrhythmias, and exacerbate coronary artery disease (CAD). It may alter myocardial function by direct toxic effects, by associated hypertension, or indirectly by altering specific electrolytes. Acute intoxication can decrease cardiac output in both alcoholic and nonalcoholic patients with preexisting cardiac disease.38

Studies have linked moderate alcohol consumption (two to four drinks per day in men and one or two in women) to a protective effect from CAD. Low to moderate alcohol consumption decreases platelet aggregation, raises plasma levels of endogenous tissue plasminogen activator,39 and lowers insulin resistance. Experimental data suggest that alcohol may have antioxidant properties, produce effects on smooth muscles through interactions with nitric oxide, and alter plasma total homocysteine levels.40,41 The produce effects on smooth muscles through interactions with heart failure (Box 185-2).43 All of these beneficial effects are lost by plasminogen activator,39 and lowers insulin resistance. Experimental
effect from CAD. Low to moderate alcohol consumption decreases in men and one or two drinks per day in women) to a protective function of the heart, produce dysrhythmias, and exacerbate coronary artery disease. It can reduce exercise tolerance, induce coronary vasoconstriction, and raise heart rate and blood pressure.45 Additive cardiovascular effects of ethanol and nicotine contribute to dysrhythmias and sudden death in patients with CAD. In one study, nearly half the patients with alcohol withdrawal had prolongation of the QT interval. Prolonged QT can precipitate a dysrhythmia, resulting in sudden death.46 There is an increased incidence of sudden death among heavy drinkers regardless of concomitant CAD or smoking.

Supraventricular (usually atrial fibrillation) and ventricular (usually transitory ventricular tachycardia) dysrhythmias, labeled “holiday heart,” have been documented in alcoholic patients who have been drinking heavily. One study reported that alcohol contributes to or causes new-onset atrial fibrillation in approximately two thirds of patients younger than 65 years. Tachydyssrhythmias as a result of episodic drinking commonly revert to sinus rhythm with abstinence and do not require immediate intervention if the patient is hemodynamically stable.

Alcohol also affects cardiac function indirectly by lowering potassium and magnesium levels. Data from the Framingham Heart Study indicate that patients with lower levels of potassium and magnesium have higher rates of dysrhythmias.47

Pulmonary Effects

Alcohol reduces the mobilization of alveolar macrophages and their bactericidal capacity. Their impairment is greatest in alcoholics with hepatic cirrhosis. In alcoholic patients, the lungs are more vulnerable to oxidative stress and injury. There is evidence that chronic alcohol consumption decreases the level of glutathione, promoting inflammation and remodeling of the lung tissue.48 These effects, along with aspiration, decreased airway sensitivity, concomitant smoking, and malnutrition, probably account for the increased incidence of pneumonia, particularly lobar pneumonia, among alcoholic patients.49 Alcohol abuse is also associated with an increased likelihood of intensive care unit admission and a longer hospital length of stay than for non-alcoholic patients with community-acquired pneumonia.50

At least 80% of alcoholics are smokers, making it difficult to distinguish between alcohol-induced and tobacco-induced injury to the lungs. The high prevalence of respiratory disease in alcoholics is largely caused by smoking. Patients with sepsis and chronic alcohol abuse are at least twice as likely to require mechanical ventilation and have a twofold to fourfold risk for development of the acute respiratory distress syndrome.50

Alcohol induces bronchospasm in some asthmatics and increases ventricular ectopy and sleep apnea in patients with chronic obstructive pulmonary disease. Alcoholic patients with hepatic cirrhosis can have hypoxemia as a result of precapillary shunting in their lungs. Hyperventilation and respiratory alkalosis are also seen with hepatic cirrhosis. One or two drinks per day has been found to decrease the risk of pulmonary embolus and deep venous thrombosis in elderly patients.31

Gastrointestinal and Hepatic Effects

Esophagus and Stomach

Alcoholic patients have a higher incidence of esophagitis, gastric cancer, and esophageal carcinoma than that in the general population. Acute alcohol ingestion also decreases lower esophageal sphincter pressure, delays gastric emptying, and disrupts the
The earliest, mildest, and most common liver change in alcoholism is the accumulation of macrovesicular fat in the hepatocytes, predominantly involving triglycerides. Alcoholic fatty liver is usually asymptomatic, associated with mild elevations of AST and ALT. It is detected by the finding of hepatomegaly on physical examination or abnormalities on ultrasonography or CT but is confirmed by liver biopsy. Fatty liver is a reversible disorder if the patient can refrain from drinking.

Alcoholic Hepatitis

Alcoholic hepatitis is more serious than fatty infiltration and develops in up to 35% of heavy drinkers. These individuals usually have right upper quadrant pain, tender enlarged liver, fever, jaundice, and abnormal liver function test results. AST levels are usually less than 400 IU/L, and ALT levels are typically less than half the AST level. Alcoholic hepatitis has a range of clinical manifestations, from mildly symptomatic hepatomegaly to fulminant hepatic failure. The severity of the disease can be estimated in the ED by a prolonged prothrombin time/international normalized ratio (INR) or with the use of discriminant factor. The ABIC (age, bilirubin, INR, creatinine) score and the Model for End-stage Liver Disease (MELD) are also helpful in predicting mortality in these patients.

Evaluation of symptomatic patients includes complete blood count, electrolyte values, blood urea nitrogen and creatinine concentrations, glucose concentration, prothrombin time/INR, liver function tests, and urinalysis. If the patient has an abnormal prothrombin time/INR and is actively bleeding, fresh frozen plasma should be started in the ED. Steroids are indicated in severe cases (encephalopathy, coagulopathy). Steroids are relatively contraindicated in patients with gastrointestinal bleeding or concurrent infection. In those for whom steroid treatment is contraindicated, pentoxifylline has been shown to be beneficial. Up to 80% of patients with alcoholic hepatitis who continue to drink eventually have cirrhosis.

### Box 185-2 Risks and Benefits of Light, Moderate, and Heavy Drinking

<table>
<thead>
<tr>
<th>Light-Moderate Drinking</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks</strong></td>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>Established</td>
<td>Decreased risk of coronary heart disease</td>
</tr>
<tr>
<td>Unresolved</td>
<td>Decreased risk of ischemic stroke</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Decreased risk of gallstones</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td><strong>Possible</strong></td>
</tr>
<tr>
<td>Established</td>
<td>Decreased risk of diabetes</td>
</tr>
<tr>
<td>Unresolved</td>
<td>Decreased risk of peripheral vascular disease</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td><strong>None</strong></td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Certain cancers</td>
<td></td>
</tr>
<tr>
<td>Accidents</td>
<td></td>
</tr>
<tr>
<td>Homicides</td>
<td></td>
</tr>
<tr>
<td>Suicides</td>
<td></td>
</tr>
<tr>
<td>Fetal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Degenerative central nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

Alcoholic Cirrhosis

Cirrhosis is the disruption of the normal architecture of the liver by scarring and regenerating nodules of parenchyma. Alcoholism is the most common cause of cirrhosis in the United States and is responsible for approximately 50% of all cirrhotic deaths. Alcoholic cirrhosis usually requires 10 to 15 years of chronic drinking, often punctuated by one or more episodes of acute alcoholic hepatitis. The clinical outcome is determined by the development of complications of portal hypertension and by hepatic dysfunction. It is unknown why hepatic damage develops in some alcoholics and not in others exposed to identical amounts of alcohol. The disorder was originally described as "nutritional cirrhosis," but it has been shown that alcohol, independent of malnutrition, produces the liver damage. Alteration of the normal hepatic architecture by fibrosis and nodule formation may eventually lead to portal hypertension. Portal hypertension may be complicated by ascites and esophageal varices. Although cirrhosis is irreversible, its progression may be halted with abstinance.

Hepatitis C antibodies are found in one third to one half of alcoholics with alcoholic liver disease, presumably from similar risk factors. Patients with alcoholic liver disease and hepatitis C have histologically more severe disease, shorter survival, and tenfold increased rates of cirrhosis and liver cancer.65 No specific medical therapy exists for alcoholic liver disease other than abstinence, proper diet, and management of the subsequent hepatic decompensation (i.e., ascites and encephalopathy). A decrease in the amount of alcohol consumed during 1 year is associated with a 60% decrease in mortality.66

Pancreatitis and Malabsorption

The association of ethanol with both acute and chronic pancreatitis is well established, but the exact pathogenesis is unclear. Hypotheses include reflux of duodenal contents and bile into the pancreatic duct, obstruction by a plug of pancreatic juice rich in proteins, and direct toxic effect of ethanol.

The diagnosis of alcoholic pancreatitis can be difficult because asymptomatic alcoholics may have an elevated amylase level. Conversely, up to 30% of patients with acute alcoholic pancreatitis have an amylase value within normal limits. Serum lipase rises after amylase, remains elevated longer, and is a more reliable indicator of alcoholic pancreatitis, especially when it is more than three times normal.67 Alcohol is the leading cause of chronic pancreatitis.

Diarrhea and impaired intestinal absorption are common problems of the chronic alcoholic. Alcohol increases small intestine transit time and decreases brush border enzyme activity. Thiamine, vitamin B12, amino acids, folic acid, and glucose have impaired absorption in alcoholics. Dietary deficiencies in folic acid and protein, pancreatic insufficiency, abnormal biliary secretion, and direct toxic effects of ethanol on the gastrointestinal tract contribute to malabsorption. Abstinence and adequate nutrition reverse the diarrhea and much of the malabsorption.58

Neurologic Effects

Neuropathy

A symmetrical sensorimotor polyneuropathy is common with chronic alcohol abuse, usually in the lower extremities. It is thought to be a combination of nutritional deficiency with thiamine or B12 deficit and a direct neurotoxic effect of alcohol. Burning pain and paresthesia are common complaints. Findings on physical examination include loss of light touch, decreased pinprick sensation, and reduced lower extremity deep tendon reflexes. Distal muscle weakness is a late finding. The neuropathy may lead to nonhealing ulcers on the feet. Treatment of alcoholic neuropathy is abstinence, adequate diet, and thiamine. Complete recovery is rare.

“Saturday night palsy” or “honeymooner’s syndrome” is a wrist drop caused by radial nerve compression. The patient usually has spent the night with the arm drooped over the back of a chair, bench, or a companion, compressing the radial nerve against the humerus and producing a neurapraxia. Loss of function due to radial nerve neurapraxia usually returns after a few weeks to months.

Wernicke-Korsakoff Syndrome

Although they are similar pathologically and caused by thiamine deficiency, Wernicke and Korsakoff syndromes are clinically distinct. Wernicke’s encephalopathy, a medical emergency with a mortality rate of 10 to 20%, remains a clinical diagnosis and is often unrecognized. Contemporary criteria require two of these signs: dietary deficiencies, ocular motor abnormalities (nystagmus is most common), cerebellar dysfunction, and either an altered mental state or mild memory impairment.68 Mental abnormalities include lethargy, inattentiveness, abulia, and impaired memory, progressing without treatment to coma.

Genetic and environmental factors may play a part in the pathogenesis of this disorder. A thiamine-dependent enzyme, transketolase, is deficient or less active in some patients who have Wernicke-Korsakoff syndrome. This may explain why the disorder develops in only a few alcoholics. Persons with transketolase deficiency are asymptomatic until they are stressed by thiamine deficiency. Protracted vomiting, inadequate diet, and malabsorption contribute to thiamine deficiency in the alcoholic.69

Korsakoff’s psychosis or amnesic state, also called alcohol-induced persisting amnestic disorder, is a disorder with recent memory impairment, inability to learn new information or to recall previously learned information, apathy, and confabulation. Although it is common, confabulation is not essential for the diagnosis. Whereas 80% of patients with acute Wernicke’s encephalopathy have Korsakoff’s syndrome, age older than 40 years and many years of heavy alcohol use are additional risk factors.70

Treatment of Wernicke-Korsakoff syndrome consists of abstinence, adequate diet, and thiamine. The ophthalmoplegia and nystagmus usually have a good response to thiamine within hours to days. The ataxia and mental changes may take days to weeks to improve and usually have a poorer prognosis. Less than 25% of patients show any real recovery, 50% show some recovery, and the remainder show no response despite adequate thiamine replacement. Because magnesium is a cofactor for this enzyme system, serum levels should be corrected. Patients with Wernicke’s syndrome require admission and aggressive thiamine and magnesium repletion.

Movement Disorders

Alcohol withdrawal is associated with tremor, ataxia, and myoclonus. Acute alcohol consumption ameliorates essential tremor and myoclonus. Persistent tremor is occasionally seen in chronic alcoholism. This alcoholic tremor may persist up to 1 year after abstinence. Although the pathophysiologic mechanism is poorly understood, studies have confirmed that essential tremor and alcoholic tremor are distinct entities.71

Alcoholic Cerebellar Degeneration

Characterized by ataxia of the extremities, cerebellar ataxia of alcoholism results in a wide-based stance and uncoordinated gait. Lower extremity involvement predominates, although the arms may rarely be involved. Pathologic changes consist of degeneration
of elements in the cerebellum, especially the Purkinje cells. The diagnosis is based on history, physical examination, and magnetic resonance imaging or CT (which shows severe cerebellar atrophy). Treatment consists of abstinence, adequate nutrition, and thiamine.72

Dementia

Some studies suggest that ethanol may offer direct neuroprotection to the brain, bearing on the apparent risk reduction of dementia in selected drinkers.73 Once again, a J-shaped curve emerges, with moderate intake reducing the risk of cognitive impairment and heavy drinking increasing it.74 Whereas small amounts of ethanol probably protect against dementia and Alzheimer’s disease but not against vascular dementia or cognitive decline, these conclusions are controversial.75

Infections

Experimental and clinical data support the conclusion that alcohol is a potent immunomodulatory agent. Chronic alcohol abuse (≥8 drinks/day) leads to immunosuppression.76 Animal and human studies have implicated acute and chronic alcohol ingestion in causing decreased serum bactericidal activity, impaired mononuclear phagocyte function, diminished cell-mediated immune functions, reduced delayed hypersensitivity reaction, and defective polymorphonuclear neutrophils. Neutropenia may be found in up to 8% of hospitalized alcoholics.77

Alcohol ingestion prevents the normal delivery (chemotaxis) of polymorphonuclear neutrophils to sites of bacterial infection. Chronic alcohol exposure depresses the development and expression of cell-mediated immunity. This depression may contribute to the high incidence of tuberculosis and head, neck, and upper gastrointestinal cancers in alcoholics. Alcohol’s suppression of macrophage function reduces the reticuloendothelial system’s ability to clear particles. This may contribute to spontaneous bacteremia, spontaneous bacterial peritonitis, and pneumonia. Primary antibody response to new antigens is also depressed. Malnutrition and liver failure also contribute to an immunocompromised state in the alcoholic.

The most common infection in alcoholism is pneumonia. Associated risk factors for pneumonia in alcoholics include smoking, decreased ciliary function, decreased surfactant production, depressed cough reflex, malnutrition, and poor oral hygiene. Although alcoholic patients may contract a variety of bacterial pneumonias, *Streptococcus pneumoniae* is still the most common organism. Periods of alcoholic stupor with incomplete glottic closure and subsequent aspiration can lead to aspiration pneumonia or lung abscess. *Klebsiella pneumoniae*, classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignant disease, and transplantation than in the chronic alcoholic. In addition, these infections now tend to be nosocomial rather than community acquired.77

Chronic alcoholism is also associated with a threefold increase of tuberculosis.78 Alcoholism itself does not seem to influence the long-term relapse rates in tuberculous patients if they have closely supervised therapy of adequate duration. Homeless alcoholic patients are an important reservoir of tuberculosis in the United States.

Spontaneous bacterial peritonitis occurs in cirrhotic patients with ascites and has a high mortality rate (50-90%). A common presentation consists of fever, abdominal pain, and leukocytosis. *Escherichia coli*, *K. pneumoniae*, and *S. pneumoniae* are the most common bacteria cultured from the ascitic fluid. Patients with new ascites and fever should have a diagnostic paracentesis as part of their evaluation.

Hepatitis C appears to be related to concomitant injection drug use rather than the direct effect of alcohol abuse. Alcoholism is associated with a high prevalence of unsafe sexual behavior and human immunodeficiency virus (HIV) seropositivity,79 with greater immunologic changes in HIV-1–positive patients who also consume alcohol.80

Fever in the chronic alcoholic may result from a vast array of causes. The most common infection remains pneumonia. Occult urinary tract infections are more common than expected. The most common noninfectious causes of fever are alcohol withdrawal and alcoholic hepatitis. A leukocytosis is associated with both, often making the differentiation from infection difficult. Both infectious and noninfectious causes may coexist, and there may be multiple sources of infection. Most febrile alcoholics without an identifiable source are best served by hospitalization.

Endocrine Effects

Alcohol dependence adversely affects many endocrine systems. Both peripheral thyroid hormone dysfunction and central hypothalamic-pituitary-thyroid axis deregulation are seen.81 Male hypogonadism and feminism are seen in chronic male alcoholics. Alcohol’s effects on both the testes and the hypothalamus decrease testosterone production in men.82 Alcohol may cause impotence by CNS sedation, secondary depression, or decreased testosterone production. Decreased testosterone, increased estrogen (in patients with liver disease), and increased prolactin can lead to decreased libido, feminization, and gynecomasia in male alcoholics and to abnormalities in lactation and menstruation in women. In female alcoholics, increased levels of testosterone and estrogen are found. Estrogen replacement therapy may increase hormonal levels threefold and thus increase the risk of cholelithiasis and breast cancer.83

Metabolic Effects

Carbohydrates

Alcohol-induced hypoglycemia occurs in 1 to 4% of intoxicated ED patients. It is more frequently seen in chronic alcoholics.84 Coma, seizures, hemiparesis, and a variety of other neurologic signs have been described in patients presenting with alcohol-induced hypoglycemia. Starvation, depletion of liver glycogen stores, decreased plasma cortisol levels, impaired release of growth hormone, and inhibition of gluconeogenesis contribute to this phenomenon.

Hyperglycemia and diabetes may be found in chronic alcoholism. Alcohol abuse can lead to chronic pancreatitis, resulting in underproduction of insulin by the damaged pancreatic cells. Alcohol also impairs peripheral glucose utilization, causing a relative insulin resistance (similar to type 2 diabetes). In diabetic patients, alcohol can induce hypoglycemia and also mask the signs of hypoglycemia. This is more prominent in the fasting state.85

Lipids

A reversible hypertriglyceridemia occurs in many chronic alcoholics. Ethanol increases hepatic synthesis of triglycerides. Abstention is necessary to reduce elevated triglyceride levels. Except for its relationship to fatty infiltration of the liver, the clinical significance of this hyperlipidemia is unknown.86

Electrolytes

Ethanol has numerous effects on electrolytes and mineral metabolism as summarized in Table 185-5. Hyponatremia and hypokalemia are common in active drinkers. Vomiting, diarrhea, magnesium
depletion, malnutrition, and metabolic alkalosis contribute to these abnormalities.

Alcoholism is the most common cause of severe magnesium deficiency in adult outpatients. Thirty percent of alcoholics are magnesium deficient as a result of malabsorption, malnutrition, diarrhea, vomiting, and increased urinary losses. Oral magnesium supplementation in chronic alcoholics improves liver function test abnormalities. 

Table 185-5 Effect of Ethanol on Mineral Metabolism

<table>
<thead>
<tr>
<th>MINERAL</th>
<th>CAUSE OF DEPLETION</th>
<th>ADDITIONAL EFFECT OF COMPARTMENT SHIFTS</th>
<th>CONSEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>Alcohol</td>
<td>↓ Hyperventilation</td>
<td>Pseudohypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>↓ Hyperaldosteronism</td>
<td>Myopathy</td>
</tr>
<tr>
<td></td>
<td>Poor intake</td>
<td>↓ Metabolic alkalosis</td>
<td>Potassium depletion</td>
</tr>
<tr>
<td></td>
<td>Phosphate depletion</td>
<td>↓ Respiratory alkalosis</td>
<td>Phosphate depletion</td>
</tr>
<tr>
<td></td>
<td>Hyperaldosteronism</td>
<td>↓ Glucose (refeeding)</td>
<td>Electrocardiographic abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Hypoparathyroidism (secondary to hypomagnesemia)</td>
<td>Seizures</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Poor intake</td>
<td>↓ Metabolic alkalosis</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>↓ Respiratory alkalosis</td>
<td>Platelet dysfunction</td>
</tr>
<tr>
<td></td>
<td>Metabolic alkalosis</td>
<td>↓ Glucose (refeeding)</td>
<td>White blood cell dysfunction</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia</td>
<td>↑ Hypoparathyroidism</td>
<td>Central nervous system dysfunction</td>
</tr>
<tr>
<td>Calcium</td>
<td>Poor intake</td>
<td>↓ Hypoparathyroidism (secondary to hypomagnesemia)</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>Steatorrhea</td>
<td>↓ Rhabdomyolysis</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td>Hypovitaminosis K</td>
<td>↓ Hypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Poor intake</td>
<td>↓ Glucose (refeeding)</td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Metabolic alkalosis</td>
<td>↓ Hyperventilation</td>
<td>Paralysis</td>
</tr>
<tr>
<td></td>
<td>Hyperaldosteronism</td>
<td>↑ Rhabdomyolysis</td>
<td>Myopathy</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
<td>Sudden death</td>
</tr>
</tbody>
</table>


* * *

Alcoholic Ketoacidosis

Alcoholic ketoacidosis most frequently occurs in severe chronic alcoholics who have had a recent binge followed 1 to 3 days later by protracted vomiting, decreased food intake, dehydration, and abstinence. Nausea, vomiting, and abdominal pain are common presenting complaints. Patients often have tachypnea, dehydration, ketonuria, and little or no glucosuria. Serum glucose levels are usually less than 200 mg/dL. Normal blood pH may be found despite ketonemia because of coexisting respiratory alkalosis and metabolic alkalosis.

The exact mechanism responsible for the increase in ketone bodies is unclear. Acute starvation superimposed on chronic malnutrition as well as release of an alcohol-induced block in ketogenesis allowing marked ketosis may explain the disorder. An increased ratio of reduced (NADH) to unreduced nicotinamide adenine dinucleotide (NAD) in the alcoholic predisposes to the accumulation of β-hydroxybutyrate and the inhibition of gluconeogenesis, which may underlie the common occurrence of hypoglycemia in alcoholic ketoacidosis.

The alcoholic patient with metabolic acidosis presents an interesting dilemma because most of these patients have an

potassium, magnesium, and phosphate depletion, empirical treatment with potassium and phosphate is discouraged. Serum levels and renal function should be determined. Unintended hyperkalemia and hyperphosphatemia can produce significant morbidity, and phosphate infusion exacerbates hypocalcemia if it is present. Because most magnesium is intracellular, a normal serum magnesium level does not rule out decreased total body magnesium stores. If the serum level is normal, total body levels may still be low. As long as renal function is adequate, empirical magnesium treatment can be considered. Abstinence and a proper diet resolve electrolyte and nutritional deficiencies in the ambulatory alcoholic patient who is healthy enough to be treated as an outpatient.
increased anion gap acidosis. Glucosuria may suggest diabetes; crystalluria can be seen in ethylene glycol poisoning; low specific gravity, proteinuria, and casts can be seen in renal failure; leukocytes and bacteria are present with urosepsis; and significant ketones in an otherwise normal urine may indicate starvation or alcoholic ketosis. Elevated levels or a very high osmolal gap (>25 mOsm/kg) is specific (88%) for methanol or ethylene glycol ingestion.

Treatment of alcoholic ketosis consists of normal saline, glucose, thiamine, and correction of hypokalemia. This can be accomplished with 5% dextrose in normal saline and either 30 mEq of potassium chloride or 30 mEq of oral potassium. Bicarbonate is seldom necessary but may be considered in the rare patient with a pH below 7.1. If no serious complicating illness is present, the ketosis is reversed in 12 to 24 hours with this treatment.

Hematologic Effects
The alcoholic presents with myriad hematologic abnormalities. The direct toxic effect of ethanol and its metabolites, secondary nutritional deficiency, and hepatic disease, individually or in combination, affect red blood cells, white blood cells, platelets, hemostasis, and the immune system. Macrocytosis is the most common hematologic manifestation of the chronic alcoholic. It may be caused by folate deficiency, reticulocytosis (the younger reticulocytes are larger), liver disease (producing an abnormal lipid coating of the red blood cell membrane), or vitamin $B_2$ deficiency. The most common condition is idiopathic macrocytosis of alcoholism.

Anemia
Several mechanisms cause anemia, which is common in the alcoholic. Megaloblastic anemia resulting from folate deficiency is the most common anemia in alcoholics. The mean corpuscular volume (MCV) is typically increased but may be normal when iron deficiency coexists. Malnutrition, inability of the cirrhotic liver to store folate, excessive urinary loss, and malabsorption decrease folate stores. Alcohol accelerates the development of megaloblastic anemia in individuals with depleted folate (MCV > 100 fL) stores by an unknown mechanism.

Iron deficiency anemia is common and usually a result of blood loss from the gastrointestinal tract. With iron deficiency anemia, the serum iron is decreased, the total serum iron-binding capacity is elevated, and serum ferritin is decreased. Alcoholics frequently have chronic inflammatory diseases, such as endocarditis, tuberculosis, empyema, lung abscess, malignant disease, and hepatic disease. These chronic inflammatory illnesses can produce the anemia of chronic disease, a mild microcytic or normocytic anemia in which the serum iron is low, but in contrast to iron deficiency, the total serum iron-binding capacity is low or low-normal, and serum ferritin is increased.

Ethanol also has a direct toxic effect on erythropoiesis. Bone marrow biopsies reveal vacuolization of erythroid precursors, resulting in decreased reticulocytosis and a reversible sideroblastic anemia. Sideroblastic anemia, usually in the presence of malnutrition with pyridoxine deficiency and folate deficiency, occurs in 25 to 30% of anemic alcoholics.

Leukocyte Abnormalities
Leukopenia is common in the alcoholic patient and has several possible causes. Sepsis, folate deficiency, and hypersplenism all lead to a decreased white blood cell count. Alcohol has a direct toxic effect on white blood cell production in the bone marrow. Granulocyte mobilization (chemotaxis) and adherence are also impaired, resulting in a decreased inflammatory response.

Platelet Disorders
Thrombocytopenia can occur with folate deficiency, sepsis, disseminated intravascular coagulation, or splenic sequestration. The direct toxic effects of alcohol decrease measured survival time and impair production of platelets in the bone marrow, but marrow toxicity will rarely reduce the platelet count below 30,000. Qualitative platelet function is also impaired. Binge drinking is associated with a reactive thrombocytosis potentially responsible for acute stroke and sudden death.

Hemostasis
Alcoholic patients have a bleeding diathesis for many reasons, including thrombocytopenia, qualitative platelet disorders, deficient production of hepatic clotting factors, gastrointestinal variceal formation, and vitamin K deficiency. A complete blood count, peripheral smear, platelet count, reticulocyte count, thrombin time, prothrombin time/INR, and partial thromboplastin time help evaluate episodes of significant bleeding. Bleeding associated with coagulation abnormalities may require fresh frozen plasma for immediate correction of coagulation factor depletion; vitamin K (10 mg IV) takes 6 to 10 hours to reverse the vitamin K–dependent factors II, VII, IX, and X. Because of poor diet and impaired hepatobiliary function, alcoholics may have insufficient vitamin K storage and benefit from vitamin K delivery. However, alcoholic patients with profound liver failure are unable to produce the precoagulation factors II, VII, IX, X, and IV, so vitamin K therapy is futile. Platelet transfusions should be started in the ED for adult patients with active bleeding when the platelet count is less than 50,000/mm³.

Oncologic Effects
Worldwide, 389,000 annual cases of cancer representing 3.6% of all cancers are alcohol related. Although alcohol itself is not carcinogenic, its metabolite, acetaldehyde, is emerging as an important contributor, being able to form stable DNA adducts, to trigger mutations in tumor suppressors and oncogenes, and to interfere with DNA repair. Smoking certainly has an additional role as a cause of neoplasia and is difficult to isolate in these studies.

Chronic alcohol use is associated with an increased incidence of upper alimentary and respiratory tract cancers with a clear dose-response relationship. Specifically, alcohol increases the risk of cancer of the mouth, pharynx, larynx, lung, esophagus, liver, and pancreas. Chronic hepatitis B infection may sensitize the liver to alcohol, producing hepatocellular carcinoma. Women who drink two to five drinks per day have a relative risk of 1.41 for invasive breast cancer compared with nondrinkers. There is also a significant increase in endometrial cancer risk among postmenopausal women who consume more than two alcoholic drinks/day. Moderate alcohol consumption leads to an increased risk of colorectal and prostate cancer.

Hypothermia
Acute alcohol ingestion is one of the most common precipitating factors for accidental hypothermia and occurs in 33 to 73% of patients presenting with a core temperature below 35°C. Alcohol exacerbates hypothermia of other causes with depressed hypothalamic thermoregulation, peripheral vasodilation producing heat loss, CNS depression, sepsis, inability to shiver, hypoglycemia, and increased risk of environmental exposure. Hypothermia may be the presentation of Wernicke's syndrome, possibly caused by lesions of the posterior hypothalamus, hypoglycemia, or sepsis. Intoxicated patients may have slower rewarming rates.
An alcoholic patient who presents with an apparent psychiatric disorder poses a diagnostic dilemma. Does the patient have a primary affective disorder with secondary alcoholism, or is the patient manifesting anxiety or depressive behavior because of alcoholism? In general, alcoholic patients with psychiatric disorders are best treated with medications that are specific for their psychiatric condition. Many alcoholics with mild depression have spontaneous resolution of symptoms with abstinence. Nevertheless, depression meeting DSM-IV criteria is best treated with antidepressants. If abstinence can be achieved, underlying psychiatric disorders are more easily diagnosed and treated.

**Psychiatric Effects**

Forty-five percent of alcohol-dependent adults are diagnosed with one or more additional psychiatric conditions during their lifetime. Of alcoholic men admitted to a psychiatric ward, approximately 40% have another psychiatric disorder unrelated to substance abuse, in particular, antisocial personality disorder, schizophrenia, mood disorders, and anxiety disorders.

Depression and antisocial personality are the two most common psychiatric disorders that correlate with alcoholism, with a prevalence of 30 to 60% in most studies. Chronic alcohol use can produce an imbalance in the serotonergic system. This imbalance may lead to increased anxiety, aggression, and depression. Interestingly, aggressive behavior is more strongly linked to depression than to alcohol dependence. Secondary depression may be caused by alcoholism, or the primary affective disorder may be present with secondary alcoholism. Mild depressive symptoms are also common in alcohol withdrawal. Antisocial individuals are at high risk for alcoholism and drug dependence, although an unstable, unhappy childhood environment appears to be more important than alcohol to the development of sociopathy. Alcohol increases the lifetime risk of suicide, with 17% of all alcoholics eventually dying by suicide. Alcoholism, major depression, and antisocial personality all predispose to suicide, and interaction among the three is particularly dangerous, but the acute risk on any day is difficult to assess.

**ALCOHOL-DRUG INTERACTIONS**

Alcohol is associated with a vast number of drug interactions (Table 185-6). These may occur through several mechanisms: altered absorption; enhanced metabolism and activated toxic metabolites through the hepatic CYP2E1 pathway; additive or synergistic effects; disulfiram-ethanol–like reactions; and congeners, compounds found in alcoholic beverages. In general, chronic alcoholism is associated with an increased rate of drug clearance as a result of enhanced metabolism and enzyme induction (cytochrome P450 system). Conversely, acute alcohol intoxication reduces clearance for other drugs, increasing their serum concentration because of competition for a shared detoxification pathway.

### Table 185-6  Effects and Mechanisms of Alcohol-Drug Interactions

<table>
<thead>
<tr>
<th>CLINICAL EFFECT</th>
<th>MECHANISM</th>
<th>DRUGS INVOLVED</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased blood alcohol levels</td>
<td>Inhibition of gastric ADH</td>
<td>Cimetidine, Ranitidine, Aspirin</td>
<td>Debatable role</td>
</tr>
<tr>
<td>Increased blood alcohol levels</td>
<td>Increased rate of gastric emptying</td>
<td>Cisapride, Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Liver damage</td>
<td>Increased hepatotoxicity (chronic or “heavy” alcohol use) Decreased metabolism of drug (acute alcohol use)</td>
<td>Acetaminophen, Isoniazid, Phenylbutazone, Narcotics, Barbiruratres, Benzodiazepines, Warfarin</td>
<td>“Heavy” drinkers can experience severe consequences even with therapeutic doses. “Binge” drinkers may have toxicity from standard doses.</td>
</tr>
<tr>
<td>May require higher dosages</td>
<td>Induction of enzymes</td>
<td>Benzodiazepines, Phenytoin, Propranolol, Warfarin</td>
<td>Chronic alcoholics</td>
</tr>
<tr>
<td>Increased bleeding time</td>
<td></td>
<td>Aspirin, NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td>Psychomotor impairment</td>
<td></td>
<td>Barbiturates, Benzodiazepines, Narcotics, Tricyclic antidepressants, Oral hypoglycemics, Antibiotics: metronidazole, sulfonamides, griseofulvin, cefoperazone, Nitroglycerin</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td>Long-acting oral hypoglycemics</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>Aldomet, Hydralazine, Nitroglycerin</td>
<td></td>
</tr>
</tbody>
</table>


ADH, alcohol dehydrogenase; NSAIDs, nonsteroidal anti-inflammatory drugs.
Enhanced Metabolism and Toxic Metabolites

Most alcohol is metabolized by ADH. A small percentage of alcohol is metabolized by the MEOS–cytochrome P450 system, which is also responsible for the metabolism of many drugs. The MEOS metabolic pathway is enhanced in chronic alcoholics, which is associated with the acceleration of the degradation of these other drugs. For example, the half-lives of warfarin, phenytoin, and isoniazid are 50% shorter in abstaining alcoholics than in nondrinkers. Barbiturates, diazepam, propranolol, and rifampin may have increased rates of clearance and shorter half-lives when they are taken by chronic alcoholics. This effect can persist for days to weeks after the cessation of drinking.58,108

Acetaminophen is the most widely used analgesic in the United States and is often recommended to alcoholic patients instead of NSAIDs to prevent gastritis. Chronic alcohol ingestion may enhance acetaminophen hepatotoxicity by accelerating the biotransformation to a toxic metabolite on the basis of a few case reports of severe or lethal acetaminophen toxicity in alcoholics taking therapeutic doses. Increased vulnerability seems to occur immediately after cessation of drinking. A synergistic effect apparently occurs with alcohol, fasting, and acetaminophen use in combination with depleted glutathione stores. A prospective observational study suggested that acute ethanol intake may be associated with a lower risk of hepatotoxicity after acetaminophen overdose.109 Greatly elevated AST levels (3000–48,000 in one series), increased ALT levels, and greatly elevated prothrombin/INR times help distinguish acetaminophen hepatotoxicity from alcoholic hepatitis.107

Additive or Synergistic Effects

Alcohol has long been known to have additive or even synergistic effects with several drugs. Acute intoxication decreases the rate of drug metabolism, which is at least partially explained by competition for the same enzymatic process in the liver. For example, ethanol has additive sedative effects when it is taken with first-generation antihistamines, barbiturates, cyclic antidepressants, benzodiazepines, phenothiazines, propanolol, and narcotics. Alcohol may also increase the activity of methyldopa and nitroglycerin. Alcohol can increase tetracycline levels by 30%. Selective serotonin reuptake inhibitors do not appear to affect alcohol kinetics or psychomotor performance.

When cocaine and ethanol are taken concomitantly, the unique metabolite, cocaethylene, is a neurologically active compound that is significantly more toxic than cocaine to the heart, liver, and brain and more addicting and more lethal than cocaine alone. Cocaethylene produces a higher incidence of confusion, lower mean Glasgow Coma Scale (GCS) scores, and a higher incidence of violent trauma and more often requires endotracheal intubation.110 Hemodynamically, these patients demonstrate an elevated heart rate (1.5-5 times normal) and blood pressure higher than with either drug alone. Sudden death is associated with 18- to 25-fold above that associated with use of cocaine alone. Plasma levels of cocaine in this combined group were higher than in those who used cocaine alone.111

Ethanol increases aspirin-induced prolongation of bleeding time and reduces the metabolism of warfarin, leading to increased anticoagulant effects. There is an increased risk of upper gastrointestinal bleeding when alcohol is combined with NSAIDs. This may be the most dangerous additive or synergistic effect of alcohol.112

Disulfiram and Similar Reactions

Most patients pretreated with disulfiram (Antabuse) who then consume even small amounts of alcohol experience an extremely unpleasant reaction. These patients have a hypersensitivity to ethanol and experience a direct response within 15 minutes and lasting 30 minutes to several hours. The reaction consists of skin flushing on the head that spreads to the trunk along with nausea, vomiting, headache, chest, and abdominal discomfort, diaphoresis, vertigo, palpitations, and confusion. A severe reaction may produce hypotension, seizures, and dysrhythmias. Disulfiram-ethanol reaction is thought to occur by the accumulation of acetaldehyde secondary to inhibition of the aldehyde dehydrogenase enzyme, which may be deficient in many Asians, or another unknown toxic factor. This incapacitating reaction has been used to discourage chronic alcohol ingestion.

A similar but milder disulfiram-ethanol–like reaction has been described when alcohol combines with several different drugs. The reaction may occur days to weeks after the last dose of medication. Four cephalosporins (cefamandole, cefoperazone, cefotetan, moxalactam), metronidazole, chloramphenicol, griseofulvin, nitrofurantoin, sulfonamides, all sulfonylureas, and chloral hydrate have produced this reaction in combination with alcohol. Life-threatening toxic reactions between griseofulvin and small amounts of alcohol have been reported.113 Treatment for disulfiram reaction is usually just observation, an antiemetic for symptoms and intravenous fluids, and rarely dopamine for severe hypotension.

Oral Hypoglycemics

Profound hypoglycemia can occur when alcohol and oral hypoglycemic agents are combined. Patients taking metformin may have an increased risk for development of lactic acidosis when it is combined with heavy drinking. A disulfiram-ethanol–like reaction has been described with many hypoglycemic agents.108

ADOLESCENT PATIENT

Although a significant percentage of children drink alcohol, there are as yet few established screening instruments for this population. The usual age at first drinking, independently of the family, is about 15 years (although this varies across cultural groups) and has not changed much in decades.6 The period of heaviest drinking is usually between 18 and 22 years of age and also does not differ between those with future alcohol-use disorders and the general population. More than 60% of teenagers, even those without alcohol-use disorders, have experienced drunkenness by the age of 18 years, and about 30% have given up events such as school or work to drink or have driven while intoxicated.

Alcohol is often associated with the three leading causes of death among youth: unintentional injury, homicide, and suicide.114 Adolescent drinking is associated with many negative consequences including suicide, carrying weapons, driving under the influence and resultant fatalities, unsafe or increased sexual activity, sexual assault, and date rape. Seventy-eight percent of high school students have tried alcohol, and 30% admit to binge drinking at least once a month.115 Binge drinking, typically defined as drinking more than five drinks on an occasion, accounts for 90% of the alcohol consumed by 12- to 17-year-old youths.114

The age at drinking onset may be an indicator for increased risk of alcohol-related injury. Adolescents who began drinking regularly before the age of 14 years are at least three times more likely to be diagnosed with alcohol dependence than are those who began drinking at the age of 21 years. In addition, adolescents who began drinking before the age of 21 years were significantly more likely, during their lives, to be injured while under the influence of alcohol.118
ELDERLY PATIENT

Unhealthy drinking is found in up to 15% of elderly (older than 65 years) ED patients. Fifty percent of older people drink alcohol, and 2 to 4% meet criteria for alcohol abuse or dependence. Common screening tests (e.g., CAGE) tend to be less sensitive in this age group. Alcohol may exacerbate underlying disease by masking anginal chest pain, worsening hypertension, and inducing dysrhythmias. However, elderly persons consuming low to moderate levels of alcohol may have a decreased risk for development of dementia and heart failure. More than 90% of people aged 65 years or older use more than one prescribed medication. Aging alters gastrointestinal absorption, lowers volume of distribution, diminishes homeostatic responses, and reduces renal and hepatic function. Elderly persons also demonstrate increased end-organ sensitivity, particularly involving the CNS, with concomitant drug use increasing their risk for alcohol and drug interactions.

A protective effect on cognitive functioning has been shown with moderate alcohol consumption, particularly in women. Moderate consumption is associated with a 38% reduced risk of dementia. Still, elderly patients are more likely to have neuropsychiatric complications of alcoholism: sleep problems, anxiety, depression, and dementia. Alcohol is involved in one third of suicides in elderly persons. Older subjects also perform less well than younger subjects on tests of perception and attention at all blood alcohol levels. This may result in an increased risk of fractures from falling and osteoporosis. However, recent evidence suggests that compared with abstinence, consumption of up to one drink per day is associated with a decreased risk of osteoporotic hip fracture and a beneficial effect of moderate alcohol consumption on bone density.

PREGNANCY

Many scientific reports confirm alcohol’s teratogenic effects. According to the National Institute on Drug Abuse, almost 19% of all children born in the United States have been exposed to alcohol during gestation. Pregnant women who report use of any alcohol, binge drinking, or frequent drinking are more likely to be older than 30 years, employed, and unmarried.

Fetal alcohol syndrome is characterized by a triad of CNS defects, including mild to moderate mental retardation; dysmorphology, involving mostly facial structures; and growth deficiencies, usually consisting of short stature and microcephaly. Fetal alcohol syndrome is now considered the most common identifiable source of mental retardation. Children exposed to prenatal alcohol exhibit increased activity levels, cognitive and attention deficits, perseverative behavior, and language and motor problems, which persist into adulthood.

Ethanol rapidly diffuses across the placenta and is distributed to all fetal tissue with a predilection for gray matter. Although infants of mothers who drink heavily have the poorest outcome, children of mothers who consume only two or three alcoholic drinks a day also display abnormalities. Even in the absence of growth retardation or congenital abnormalities, children born to women who consume excessive alcohol during pregnancy appear to be at increased risk for attention deficit disorders. These findings are referred to as fetal alcohol effects.

Whereas there is no known safe amount of consumption during pregnancy, in a cohort study of more than 5000 patients observed for 14 years, an average of less than one drink per day in early or late pregnancy showed no measurable impact on a child’s learning or cognitive functioning. Adverse outcomes in this study were associated with an average of more than one drink per day, binge drinking, and consumption of alcohol later in pregnancy. The American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning a pregnancy.

TRAUMA

The single greatest contributor to alcohol-related mortality in the United States is unintentional injury, accounting for approximately 26,000 deaths per year. The importance of alcohol misuse as a precursor to serious injury is widely accepted enough that since 2006 the American College of Surgeons Committee on Trauma requires screening for problem drinking for designation as a level I or level II trauma center. In addition, level I trauma centers must provide an intervention for problem drinkers identified. Alcohol and trauma are inextricably linked. Independently, the tragic effects of each are numerous; in combination, they are staggering. Injury is the leading cause of death between the ages of 1 and 44 years, accounting for more than 50 million injuries per year. In the United States, alcohol is the major risk factor for virtually all categories of intentional and unintentional injury. Besides increasing the frequency and severity of injury, alcohol significantly complicates the management of the trauma victim. Alcohol intoxication often complicates the initial assessment of injury severity, resulting in an increased need for invasive diagnostic and therapeutic procedures (e.g., intubation, CT scan, intracranial pressure monitoring).

Alcohol may diminish the patient’s capacity to respond to hemorrhagic shock by altering hemodynamic effects and acid-base balance. Volume depletion as a result of the diuretic effect of alcohol or vomiting can impair the reserve of the intoxicated trauma patient. Peripheral vasodilation caused by alcohol may contribute to hypotension and hypothermia. Although these effects may be minimal, they underscore the need for early and adequate fluid resuscitation in these patients. Intoxicated patients with severe non-neurologic trauma may have lower blood pressures and carbon dioxide levels (indicative of a compensatory hyperventilation) on hospital arrival compared with sober patients. More important, a poorly understood cardiac depressant effect also increases the depth of shock and volume requirements for resuscitation. Alcohol-induced skin vasodilation may be accompanied by an increase in skeletal muscle, mesenteric, and renal bed constriction and left ventricular stroke work. Thus the overall effect on systemic vascular resistance and blood pressure may be balanced.

Intoxication renders the signs and symptoms of intra-abdominal and retroperitoneal injury less reliable than usual. If the risk of an intra-abdominal injury exists, further evaluation (e.g., ultrasonography, CT) should be considered. Alcohol intoxication predisposes to abdominal wall laxity and thus less protection from blunt trauma. These patients are also likely to have full stomachs, increasing the risk of gastric injury after trauma and predisposing to vomiting and aspiration, especially during airway management. The fatty liver changes of alcoholism can result in hepateomegaly. Portal hypertension in alcoholics may produce splenomegaly. These organs can become more vulnerable to the effects of trauma because of their enlarged size, protrusion beneath the protection of the ribs, and increased intracapsular pressure.

Alcohol intoxication contributes to CNS injury in many ways. It is associated with aggressive behavior, impaired reflexes and coordination, and inappropriate avoidance responses. A higher degree of trauma to the spinal cord and much worse neurologic and functional recovery occur in patients who are intoxicated during trauma compared with sober patients.
Experimental evidence suggests that alcohol acts synergistically with mechanical injury of the spinal cord to amplify the trauma response by increasing edema formation within the contused tissue.\textsuperscript{135}

No consensus exists on the indications for an emergency CT scan in patients with “minor head injury” (loss of consciousness, post-traumatic amnesia, GCS score of 14 to 15, normal findings on neurologic examination). One disturbing prospective study found that the GCS score and 1 hour of observation were unable to predict abnormal head CT scans in intoxicated patients with minor head trauma. Patients with signs of head trauma and focal or generalized seizures need an urgent CT scan. CT scans of the head should be performed for any patient with deteriorating mental status, focal neurologic findings, new-onset seizures even without obvious signs of history of trauma, failure to improve over time, or mental status changes out of proportion to the degree of intoxication.\textsuperscript{136}

The good news is that during the past 20 years, there has been a decline in the number of alcohol-related fatalities. Five states (Hawaii, Illinois, Indiana, Pennsylvania, and Utah) have enacted mandatory hospital and provider reporting laws.\textsuperscript{137}

**ADMISSION GUIDELINES AND DISPOSITION**

Most alcoholics suffer from a combination of medical, psychiatric, and social problems. Hospitalization is often necessary to diagnose and to treat these multiple problems. Moreover, with alcoholics who are no longer able to care for themselves, hospitalization is often dictated for this reason alone. Unfortunately, many managed care and Medicaid plans limit or do not cover inpatient detoxification. In choosing medical versus psychiatric admission, a medical illness usually takes priority. Optimal outpatient therapy for chronic alcoholics includes concerned family or friends to ensure that the patients take their medications properly, keep follow-up appointments, abstain from alcohol, and maintain an adequate diet. Alcoholic patients who undergo outpatient treatment need close supervision; therefore, a follow-up clinic appointment within 24 to 48 hours should be considered.

**Acute Intoxication**

Acute intoxication alone seldom requires admission. However, combined alcohol-drug overdose or associated medical, psychiatric, or social problems may require hospitalization. Acute alcohol intoxication is a diagnosis of exclusion reached after adequate observation to ensure that the altered mental status resolves.

Alcohol levels that may be tolerated by an adult can be lethal in children. It is prudent to admit children with acute intoxication unless close psychosocial follow-up can be ensured. Children presenting with hypoglycemia or medical complications should be admitted. Child abuse or neglect should be considered.

**Alcohol Withdrawal**

Patients with signs of major withdrawal (fever, hallucinations, confusion, extreme agitation) require admission. Patients with mild alcohol withdrawal can be observed in the ED. After 4 to 6 hours of observation and treatment, the alert, oriented patient whose vital signs, physical examination findings, and results of appropriate laboratory analysis are within normal limits may be released with appropriate medications and aftercare instructions. Nevertheless, the patient requires treatment for the underlying disease of alcoholism and should be advised or referred accordingly.

**Seizures**

Patients experiencing their first alcohol-related seizure may be admitted. Admission allows initiation of drug therapy, diagnostic evaluation, and continued monitoring of the patient’s status. However, the alcoholic patient with a first-time alcohol-related seizure may be discharged to a suitable social situation when the patient’s alcohol withdrawal is mild and controlled either by supportive care or with low-dose benzodiazepines; the diagnostic workup, including a head CT scan, is unremarkable; the patient has had fewer than two seizures; and the patient has been observed to be alert and oriented, with normal vital signs, physical examination findings, and laboratory study results, during the 6 hours since the last seizure, and appropriate outpatient follow-up can be ensured.

Patients with a documented history of alcohol-related seizure can be discharged if they have had no more than two alcohol-related seizures during a 6-hour period with a lucid interval between seizures and are observed to be seizure free and at baseline mental and physical status for at least 6 hours after their last alcohol-related seizure. Three to five brief, self-limited seizures may occur with alcohol withdrawal seizure. Nevertheless, admission for patients with two or more seizures is advised because of the potential for deterioration to status epilepticus. This is especially appropriate in the malnourished, immunocompromised, homeless, or noncompliant alcoholic patient.

Patients with partial seizures or focal neurologic findings on physical examination require admission unless these findings are previously documented. Patients with seizures associated with head trauma or with mixed alcohol-drug withdrawal are admitted. Status epilepticus or recurrent seizures during ED observation indicate a lack of seizure control also requiring hospitalization.

**Psychiatric and Social Problems**

Alcoholic patients requiring admission with acute intoxication, alcohol-related seizure, alcohol withdrawal, or medical or surgical disorders are usually best managed in acute care units rather than by a general psychiatric service. Some psychiatric and social conditions in the alcoholic can be better handled on a general psychiatric unit: psychosis, exacerbation of schizophrenia, depression with suicidal tendencies, any patient who is a danger to self or others, or alcoholic hallucinosis with an otherwise clear sensorium.

Patients who are no longer able to care for themselves may also require admission. Although these patients’ ultimate destination is a rehabilitation center or a board-and-care program, hospitalization may be necessary to rule out medical or psychiatric illness and to treat impending withdrawal symptoms. Patients who wish to stop drinking are usually admitted to a detoxification unit for treatment of impending withdrawal. Data and interest are increasing for outpatient drug therapy in alcohol dependence. The U.S. Food and Drug Administration has approved disulfiram, naltrexone, acamprosate, and topiramate for treatment of alcohol dependence.\textsuperscript{43} There is growing evidence that patients with alcohol dependence who carry a particular variant of an opioid receptor gene are more likely to respond to naltrexone, raising the possibility that genetic tests may one day guide medication selection.\textsuperscript{138} Naltrexone, ondansetron, acamprosate, and topiramate plus naltrexone have had mixed results facilitating abstinence.\textsuperscript{139,140} The role of medications in combination with behavioral therapy is actively investigated.\textsuperscript{141,142}

Several other medications are under active study and are sometimes prescribed for alcoholism treatment on an unapproved or off-label basis. Baclofen, because of its anticroaving action and
safety, could have an important role for treatment of alcohol-dependent patients with advanced liver disease.\textsuperscript{143} Gabapentin is used as monotherapy or as an add-on pharmacotherapy in outpatient settings in the control of alcohol consumption and craving and in helping patients achieve abstinence.\textsuperscript{144} Ondansetron may show benefit in early-onset but not in late-onset alcoholics.\textsuperscript{145}

Brief intervention has reduced alcohol consumption in some well-designed ED studies but not in others.\textsuperscript{146,147} Alcohol dependence and a positive screen for alcohol-related injuries are decreased after screening and brief intervention.\textsuperscript{148} Internet-based interventions show promise for reducing alcohol consumption, especially among those meeting criteria for hazardous or harmful drinking.\textsuperscript{149} Telephone contact after the ED visit may be another effective tool to screen injured patients for hazardous drinking and to offer brief intervention while avoiding interruptions to patient flow.\textsuperscript{150} Referral and brief intervention are warranted.\textsuperscript{151} Most communities have either an Alcoholics Anonymous (AA) chapter or a treatment center for anyone who desires help with alcohol. In smaller communities, clergy or social workers can usually arrange rehabilitation.

Alcohol kills—it kills the alcoholic and it kills unintended victims by the acts of inebriated persons. Whereas medical, psychological, or social problems bring the alcoholic to the ED, the underlying problem is alcoholism and the ultimate goal is abstinence. This disease surely progresses if alcoholism is not first recognized and the patient is never given the opportunity to participate in a rehabilitation program.\textsuperscript{152} The emergency physician can intervene on behalf of the patient and the public.

**KEY CONCEPTS**

- Moderate alcohol consumption is defined as one or two drinks per day for men and one drink for women.
- Benzodiazepines are the main treatment of alcohol withdrawal and alcohol withdrawal seizures.
- Inappropriate alcohol consumption or alcohol dependence should be considered in patients in almost any clinical situation, including trauma, potential drug-alcohol reactions, pneumonia, cardiomyopathy, new-onset atrial fibrillation, hepatitis, gastrointestinal bleeding, pancreatitis, altered mental status, depression, suicide, magnesium deficiency, and anemia.
- Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after the cessation of or significant decrease in alcohol intake.
- Major alcohol withdrawal occurs after 24 hours and usually peaks at 50 hours (but occasionally takes up to 5 days) after the decrease or termination of drinking.
- Delirium tremens is the extreme end of the alcohol withdrawal spectrum and consists of gross tremor, profound confusion, fever, incontinence, and frightening visual hallucinations.
- Not all alcohol-related seizures are alcohol withdrawal seizures.
- Brief intervention in the emergency department can decrease drinking and its long-term consequences.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.
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