CHAPTER 63 SEDATION AND NEUROMUSCULAR BLOCKADE

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PERSPECTIVE

Anxiety is one of the human emotions that help us anticipate and prepare for real or perceived threats. Anxiety results in the release of endogenous catecholamines with an accompanying increase in heart rate, blood pressure, tremulousness, and so on. In some critically ill patients, anxiety can lead to agitation, i.e., anxiety coupled with confusion and movement and, if the confusion is severe enough, delirium. Increasingly, there is recognition that the spectrum of anxiety, agitation, and delirium may be a manifestation of the effects of the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), with the brain being the end organ affected. With this recognition of the significance of anxiety has come an increasing attention to monitoring its severity, as well as treatment and assessment of the effects of therapy.

The lung is the most frequently injured organ in patients with MODS, resulting in acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). Patients with ALI and ARDS require intubation and mechanical ventilation, and, with modes of mechanical ventilation adjusted to deliver low tidal volumes with resultant hypercarbia, patients are more likely to become agitated. In such patients in whom sedation is inadequate, neuromuscular blocking agents (NMBAs) may be required. These medications should always be administered cautiously, with daily drug “holidays,” which permit the clinician caring for the patient to determine if the NMA is still required.

FEATURES

Anxiety

Anxiety is often described as a heightened sense of awareness, apprehension, dread, or anticipation. The latter is an important characteristic, for anxiety is an emotional state; the individual “anticipates” a threat, and anxiety prepares the individual for “fight or flight.” Anxiety has its anatomic construct in the limbic system and is associated with the release of catecholamines, which lead to the tremulousness, sweating, tachycardia, and tachypnea—all the hallmarks of anxiety. In its extreme, an individual may have a “panic attack.”

Oftentimes when clinicians round on patients in the ICU, they find a patient who looks distressed, and blood pressure and heart rate are elevated. We commonly assume that the patient is in pain, and yet frequently, anxiety is the problem. Interestingly, it is the easiest way to separate these two perceptions is to ask the patient. As part of the daily evaluation of patients in the ICU, they should be asked if they are anxious, if they are in pain, and if they are “getting enough air to breathe?” The latter two complaints are likely to exacerbate anxiety, along with several other experiences that ICU patients may have (Table 63.1). The treatment for pain and anxiety are often the same, but for patients without pain, the treatment algorithm is different (see below). However, anxiety and pain are often a continuum, with the perception of one increasing the perception of the other.

Anxiety may lead to insomnia, a common problem in the ICU, and insomnia (and sleep deprivation) can increase the perception of anxiety (1). Sleep interruption occurs for several reasons, starting with excessive noise levels in many ICUs at night, patient care activities, measurement of vital signs, laboratory tests, radiographs, and so on. Patients who are intubated and mechanically ventilated are even more likely to have interrupted sleep, along with experiencing discomfort from the mode of mechanical ventilation and/or tracheal suctioning, as well as hypercarbia and hypoxia. In surveys of patients discharged from the ICU, patients recall feelings of terror, nervousness, and insomnia (2). Older patients, because they have less organ reserve, are more at risk of developing problems; depending on the extent of chronic health problems, the acute illness, and medications the patients receive, they are more at risk of cognitive dysfunction (3), which increases the risk of developing agitation and delirium (4).

Agitation

In the 2001 Agitation Consensus Conference, agitation was described as “continual movement characterized by constant fidgeting, moving from side to side, pulling at dressings and bed sheets, and attempting to remove catheters or other tubes” (5). Agitation is associated with some degree of cognitive impairment—disorientation, confusion, confabulation, and so on. Agitation is different from anxiety because the agitated patient displays purposeless movement and has some degree of cognitive dysfunction. For the reasons mentioned about removal of invasive devices, agitated patients are at risk of injuring themselves and, in some circumstances, injuring health care providers. Factors associated with agitation (6) include advanced age, neuropsychiatric comorbidities, seriousness of illness, pain, and some drugs that, when given to ICU patients, have unrecognized interactions and side effects. Agitation is associated with an increased length of stay, iatrogenic infections,
and self-extubation (6). Many believe that prolonged anxiety, depending on the cause, if left untreated, can lead to agitation (5). Most of the tools to monitor agitation and the effects of therapeutic interventions are listed in Table 63.2 (7–12). However, because patient movement is one of the hallmarks of agitation, some clinicians use a variant of the Ramsay Sedation Scale and the Motor Activity Assessment Scale (Table 63.3) to monitor for agitation (13).

### Delirium

The hallmark of delirium is cognitive dysfunction, most commonly manifested as disorientation in a patient who is critically ill. In the past, such patients were diagnosed as having “ICU syndrome,” a diagnosis of exclusion. Heightened awareness has resulted in several studies that have examined the prevalence (14), types (15), consequences (16), and the diagnosis and management (17) of delirium.

In a coronary care unit, the prevalence of delirium can run as low as 7% (14), whereas in a medical ICU, it may run as high as 70% to 80% (15). Delirious patients may manifest a variety of psychomotor behavior, from hypoactive (listlessness) to hyperactive (combative behavior), with a mixed picture also seen (15). Independent of the motor type, the delirious patient is at risk for developing long-term cognitive impairment (18), a greater length of ICU and hospital stay, and an increased mortality (16). Patients frequently cycle between overly sedated states to hyperactive, agitated states. Management can be difficult, as some medications commonly given to sedate patients have also been associated with an increased incidence of delirium (19).

Anxiety, agitation, and delirium require recognition (20) and education of health care professionals (17) so we can identify at-risk patients and improve treatment.

### EVALUATION

Although anxiety is a valid emotional response to hospitalization in an ICU, an overexuberant response to the stressors in the ICU environment can be detrimental. Anxious patients have an increase in the incidence of several disease states/processes (Table 63.4) (21–23). Patients should be examined on a daily basis, particularly to look for certain signs that increase the likelihood of anxiety (Table 63.5). The laboratory evaluation (Table 63.6) is also helpful in determining if the patient is, indeed, hypercapnic, septic, or has increased or decreased concentrations of electrolytes in the blood that often correlate with an increased risk of neurologic dysfunction.

### TABLE 63.1

<table>
<thead>
<tr>
<th>EXPERIENCES THAT INCREASE PATIENT ANXIETY IN THE INTENSIVE CARE UNIT</th>
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<tbody>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Insomnia</td>
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<tr>
<td>Temperature extremes</td>
</tr>
<tr>
<td>Loneliness</td>
</tr>
<tr>
<td>Clinical outlook</td>
</tr>
<tr>
<td>Physical restraints</td>
</tr>
<tr>
<td>Tracheal suctioning</td>
</tr>
<tr>
<td>Distended bladder</td>
</tr>
<tr>
<td>Invasive lines/devices</td>
</tr>
<tr>
<td>Loss of control/autonomy</td>
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### TABLE 63.2

<table>
<thead>
<tr>
<th>SEDATION SCALES</th>
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<tbody>
<tr>
<td>ATICE Adaptation to the Intensive Care Environment (7)</td>
</tr>
<tr>
<td>MSAT Minnesota Sedation Assessment Tool (8)</td>
</tr>
<tr>
<td>RSS Ramsay Sedation Scale (9)</td>
</tr>
<tr>
<td>RASS Richmond Agitation-Sedation Scale (10)</td>
</tr>
<tr>
<td>SAS Sedation Agitation Scale (11)</td>
</tr>
<tr>
<td>VICS Vancouver Interaction and Calmness Scale (12)</td>
</tr>
</tbody>
</table>

### TABLE 63.3

<table>
<thead>
<tr>
<th>MOTOR ACTIVITY ASSESSMENT SCALE</th>
<th>Description</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>0 Unresponsive</td>
<td>Does not move with noxious stimulus</td>
<td></td>
</tr>
<tr>
<td>1 Responsive only to noxious stimulus</td>
<td>Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus</td>
<td></td>
</tr>
<tr>
<td>2 Responsive to touch or name</td>
<td>Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is loudly spoken</td>
<td></td>
</tr>
<tr>
<td>3 Calm and cooperative</td>
<td>No external stimulus is required to elicit movement, and the patient is adjusting sheets or clothes purposefully and follows commands</td>
<td></td>
</tr>
<tr>
<td>4 Restless and cooperative</td>
<td>No external stimulus is required to elicit movement, and patient is picking at sheets or clothes or uncovering self and follows commands</td>
<td></td>
</tr>
<tr>
<td>5 Agitated</td>
<td>No external stimulus is required to elicit movement, and patient is attempting to sit up or moves limbs out of bed and does not consistently follow commands</td>
<td></td>
</tr>
<tr>
<td>6 Dangerously agitated,</td>
<td>No external stimulus is required to elicit movement, and patient is pulling at tubes or catheters or thrashing side to side or striking at staff or trying to climb out of bed and does not calm down when asked</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 63.4
ANXIETY ASSOCIATED WITH AN INCREASED INCIDENCE OF SEVERAL DISEASE STATES/PROCESSES

- Myocardial ischemia (21)
- Asthma (22)
- Pain (23)
- Agitation (24)
- Delirium (23)

TABLE 63.5
PHYSICAL EXAMINATION
- Tachypnea
- Tachycardia
- Confusion
- Abdominal distention (ileus, full bladder)
- Movement

TABLE 63.6
LABORATORY EVALUATION
- Complete blood count (anemia, leukocytosis/leukopenia)
- Arterial blood gases (hypoxia, hypocarbia/hypercapnia)
- Electrolytes
- Glucose
- Creatinine/blood urea nitrogen

*To include calcium and magnesium.

TABLE 63.7
NONPHARMACOLOGIC THERAPY FOR ANXIETY-PRODUCING EVENTS

- Thorough explanation of situation/findings
- Reassurance
- Increased presence of family members (26)
- Decreased noise (27)
- Decreased nocturnal interruptions
- Assisted ventilation for hypercarbia
- Cardioversion for hemodynamically significant tachyarrhythmias
- Decrease/top tube feedings if (partial) ileus
- Foley catheter for bladder distention
- Re-establishment of sleep cycle (28)

TABLE 63.8
THERAPY FOR ANXIETY-PRODUCING EVENTS

- Supplemental oxygen for hypoxia
- Minimize dose of supplemental catecholamines
- Continue any of patients’ psychotropic medications, if appropriate
- Opioids
- Benzodiazepines
- Haloperidol
- Propofol
- Dexmedetomidine
- Ketamine

When a patient admits to excessive anxiety, one should first attempt to decrease the anxiety through nonpharmacologic means (Table 63.7) (24–28). First and foremost is the recognition that the environment in the ICU must be calm and nurturing, with attention to such details as room temperature, noise levels, and sleep disturbance—the bane of most modern ICUs.

Approximately 60% to 70% of patients who reside in the ICU for greater than 48 hours will require pharmacologic therapy (Table 63.8). Of the possible agents, opioids, benzodiazepines, haloperidol, propofol, and dexmedetomidine are the mainstays of treatment.

TREATMENT

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) do not have sedative properties, but to the extent that they decrease pain, they do decrease pain-associated anxiety. NSAIDs would most likely be contraindicated in ICU patients because of their side effects. However, when cyclo-oxygenase (COX)-2 inhibitors, which have fewer side effects, are coupled with gabapentin or its precursor, pregabalin, they have analgesic and sedative properties if given preoperatively per os to patients who are anticipated to be admitted postoperatively to the ICU. In one study, a combination of 400 mg of celecoxib and 150 mg of pregabalin improved patients’ sedation levels by approximately 33% for up to 24 hours postoperatively (29).

**Opioids**

Because pain or discomfort (from tracheal tube suctioning, nasogastric tubes, or Foley catheters) is a frequent, confounding factor for anxious patients, analgesics are often administered, usually via continuous intravenous infusions. Importantly, opioids have not only analgesic but also anxiolytic properties (30). Morphine has anxiolytic properties, but is not nearly as effective as newer opioids, and, because of the buildup of active metabolites in patients with renal insufficiency, it is not recommended for patients in the ICU. Fentanyl and remifentanil are over 90% effective in providing adequate sedation for intubated and mechanically ventilated patients in the ICU (31). Because of equal efficacy and differences in cost, fentanyl is recommended in most patients, except those with significant renal/hepatic impairment (Table 63.9).

**TABLE 63.9**

<table>
<thead>
<tr>
<th>OPIOIDS AS SEDATIVE DRUGS IN THE INTENSIVE CARE UNIT</th>
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</thead>
<tbody>
<tr>
<td><strong>Bolus dose</strong></td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
<tr>
<td>Remifentanil</td>
</tr>
</tbody>
</table>

Side effects: Hypotension, nausea and vomiting, respiratory depression.
**Benzodiazepines**

Benzodiazepines, which potentiate the effects of gamma-aminobutyric acid via the benzodiazepine receptor and suppress central nervous system (CNS) activity (32), are administered to provide sedation in the ICU. They were observed to have sedative properties in animals (33), which led to their use because of their hypnotic, muscle-relaxant, anticonvulsive, and antegrade and variable retrograde amnestic properties. The benzodiazepines do not have analgesic properties, but similar to the opioids, they can and do produce respiratory depression in a dose-dependent fashion.

In critically ill patients, many of whom have MODS, because benzodiazepines are metabolized in the liver with the metabolites excreted by the kidneys, the half-lives (t1/2) are prolonged, and active metabolites may accumulate. Most commonly, benzodiazepines are administered by continuous infusion, so the context-sensitive t1/2 is more germane but independent of the method of administration because of the potential prolonged effect, a daily “off” period should be established to avoid overdosage (see below). The most commonly used benzodiazepines in the ICU are diazepam, midazolam, and lorazepam (Table 63.10).

**Diazepam**

Diazepam is an effective sedative-hypnotic with amnestic properties. Because diazepam is irritating when injected intramuscularly or intravenously and due to its long half-life, it is not often administered in the ICU.

**Lorazepam**

Lorazepam is an intermediate-acting benzodiazepine with a t1/2 of 10 to 12 hours. Respiratory and cardiovascular effects of lorazepam are no different than those for diazepam and midazolam. Lorazepam is recommended for long-term (greater than 24 hours) administration for patients who are critically ill (34). This may seem surprising because of its t1/2, but because its metabolites have no clinical activity and there is less interindividual variability (35), recovery from lorazepam, compared to midazolam, following long-term administration is no different (36) and is associated with pharmacoeconomic benefits (37).

**Midazolam**

Midazolam is the shortest acting of those benzodiazepines used in the ICU, with a t1/2 of 1 to 5 hours. Midazolam causes no pain or phlebitis following intravenous administration and is two to four times more potent than diazepam. These characteristics make midazolam an ideal drug for continuous intravenous infusion, as it has rapid onset and relatively rapid offset. It is recommended for short-term use (34); long-term (>24–48 hours) use is problematic because gamma-hydroxy midazolam, the main metabolite, with sedative properties almost identical to the parent compound, accumulates in critically ill patients with decreased albumin levels and decreased renal function, leading to prolonged sedation once the infusion is discontinued. Typically, when administering midazolam for anxiolysis or sedative-hypnotic reasons, 1-mg incremental increases are given intravenously as a bolus, with repeated boluses administered every 5 minutes to effect. A continuous infusion of 0.3 to 5 mg/hour can then be started and continued for as long as necessary.

**Additional Cautions and Recommendations Regarding Benzodiazepine Use**

The United States Food and Drug Administration (FDA) has administered black box warnings for benzodiazepines to the effect that anyone administering these respiratory depressants must be skilled in airway management and resuscitation. Similarly, one must have the benzodiazepine antagonist flumazenil—a drug that reverses all known CNS effects of benzodiazepines—available in the ICU. Flumazenil has maximum effect within 5 to 10 minutes after intravenous administration and has a mean t1/2 of approximately 1 hour. Typically, it is given in 0.1- to 0.2-mg increments, repeated every 3 to 10 minutes, to a total dose of 1 mg. Because of the active metabolites of diazepam and midazolam, these benzodiazepines should be used with extra caution in patients with renal insufficiency, as the active metabolites will accumulate. Furthermore, although these medications are often given as intravenous infusions, because of the increasing emphasis on cost efficacy in our ICUs, patients who are able to take medications per os should, when feasible, have their intravenous medication discontinued and an oral benzodiazepine started (38). Furthermore, despite the guidelines that have previously been established (34), not all studies have shown a benefit of lorazepam compared to midazolam for long-term administration; Barr et al. (39) found in 24 patients that those who received midazolam for greater than 72 hours had emergence times from their drug-induced hypnotic state that were shorter than those patients who received lorazepam. Additional research in this area of finding the best short-term and long-term sedative agents is recommended (40).

It is further recommended and supported by clinical studies that patients who are on long-term (greater than 24 hours)

### TABLE 63.10

<table>
<thead>
<tr>
<th>BENZODIAZEPINES USED FOR ANXIOLYSIS IN THE INTENSIVE CARE UNIT</th>
<th>Drug (classification)</th>
<th>t1/2 (h)</th>
<th>Active metabolite(s) (t1/2)</th>
<th>Intermittent IV bolus</th>
<th>Continuous IV infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam (long-acting)</td>
<td>20–50</td>
<td>Desmethyldiazepam (30–200)</td>
<td>1–2 mg (max 0.1–0.2 mg/kg)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (intermittent-acting)</td>
<td>10–20</td>
<td>None*</td>
<td>0.5–2 mg (max 4 mg)</td>
<td>Up to 0.025 mg/h</td>
<td></td>
</tr>
<tr>
<td>Midazolam (short-acting)</td>
<td>1–2.5</td>
<td>1-hydroxy midazolam</td>
<td>0.5–2 mg (max 0.1 mg/kg)</td>
<td>Up to 0.05 mg/h</td>
<td></td>
</tr>
</tbody>
</table>

*3-0-phenolic glucuronide is the inactive metabolite.
infusions of benzodiazepines benefit from a daily drug “holiday” (41), i.e., infusion stopped typically every morning around 7:00 or 8:00 a.m., and the infusion remains off until the patient exhibits symptoms or signs that warrant restarting the infusion. The possibility of overdosing is decreased if patients are assessed on a regular basis for their degree of sedation. There are several tools that can be used to monitor the adequacy of sedation, beginning with the Ramsey Sedation Scale (Table 63.2) (7–12). The team that manages patients in the ICU who require intravenous administration of benzodiazepines should follow a protocol for the administration of these drugs and use a tool with which they are familiar to monitor the degree of sedation. As a final caveat, once these medications are completely discontinued, up to one third of the patients will exhibit signs of withdrawal (42). In these patients, it is common practice to discontinue the benzodiazepines slowly over several days, treating the side effects of withdrawal—tachycardia and hypertension—with a beta-blocker or an alternative drug, including chronic low doses of benzodiazepines in those patients in whom beta-blockers are contraindicated.

**Propofol**

Propofol (di-isopropylphenol) is a highly lipophilic compound formulated in an isotonic oil in water emulsion (Intralipid) that is unrelated to other sedative/anesthetic agents (43). Because it is formulated in lipid emulsion, side effects include hypertriglyceridemia and bacterial contamination of infusions. The addition of ethylenediaminetetraacetic acid (EDTA) or bisulfit as preservatives decreases the incidence of bacterial overgrowth. A rare side effect is the propofol infusion syndrome (44), metabolic acidosis, and ventricular fibrillation in children and in young adults with neurologic injury receiving greater than 100 μg/kg per minute of propofol for greater than 12 to 24 hours. Propofol is now probably the most commonly used intravenous anesthsia induction agent, and is being advocated by some for use in moderate sedation (endoscopy suite) protocols (45). Because of its rapid onset and offset, few residual aftereffects, and low side-effect profile, it is often used for short-term sedation in the ICU. As the cost of the product has decreased, it is more commonly administered for long-term sedation in the ICU. Propofol has no analgesic properties, so for patients with pain, an analgesic drug should be coadministered. Propofol has also been used to treat status epilepticus (46) and to induce sleep in the ICU (47).

**Dexmedetomidine**

Alpha-2 (α2) agonists, such as methyldopa and clonidine, have long been known to have sedative properties; in fact, clonidine is administered epidurally for its antinoicceptive effects in the spinal cord. Dexmedetomidine is an α2 agonist that acts by binding to α2 receptors in the locus ceruleus with a high α2/α1 ratio of approximately 1,620:1, approximately seven times more avidly than clonidine. Binding to the α2 receptor releases norepinephrine and decreases sympathetic activity; the net effect is sedation, analgesia, and amnesia. Dexmedetomidine is unique compared to the other anxiolytic drugs because it is not associated with respiratory depression. However, because of its central alpha agonist, hypotension can and does occur. Fortunately, low-dose dexmedetomidine (6 μg/kg per hour for 10 minutes followed by an infusion of 0.2 μg/kg per hour) is as effective as higher doses (0.6 μg/kg per hour), with fewer side effects (48,53). There is concern that if dexmedetomidine is used for greater than 24 hours and discontinued abruptly, that a hyperdynamic state will ensue similar to the one that develops when clonidine is stopped abruptly following long-term use; but cases of cardiac arrest, though reported, are uncommon. Dexmedetomidine has been approved by the FDA for 24-hour use (54), although many clinicians are using it for longer than 24 hours. Of the currently used anxiolytic medications, dexmedetomidine is the most expensive.
Butyrophenones

Butyrophenones are neuroleptic drugs that are also known as antipsychotic drugs or major tranquilizers. They induce apathy, a state of mental detachment in patients with psychoses or delirium. By inhibiting dopamine-mediated neurotransmissions in the CNS, they decrease the frequency of hallucinations, delusions, and other abnormal thoughts. Patients become so detached from their environment that they develop a characteristic flat affect. Butyrophenones are active in the chemoreceptor trigger zone in the brainstem and thus are effective antianemics; they are also used to treat hiccups and are used as synergistic anxiolytic drugs when used with benzodiazepines.

Of the butyrophenones, haloperidol is the drug used most often to treat delirium in the ICU. Haloperidol has a wide therapeutic margin but has important side effects including hypotension, extrapyramidal symptoms, anticholinergic effects (tachycardia, urinary retention, ileus), neuroleptic malignant syndrome, and seizures. These side effects are rare. Hypotension following a dose of haloperidol is almost always seen in patients who are hypovolemic. Extrapyramidal symptoms are more often seen in younger patients and in patients with depleted dopamine stores, e.g., patients with Parkinson disease.

The initial dose of haloperidol is usually 0.5 to 2 mg administered parenterally, although depending on the patient’s size, age, and degree of agitation/delirium, 5 mg can be given. Haloperidol has a slow onset, so peak effects may not be seen for 15 to 30 minutes. Repeat doses then should be administered at 30- to 60-minute intervals. Recurrence of agitation or an increase in delirium is an indication for repeat doses, which may be increased if the initial dose was inadequate. Tardive dyskinesia or neuroleptic malignant syndrome can occur even during the short duration of therapy used in the ICU.

Haloperidol, because of its anticholinergic effects, may prolong the QT in a dose-dependent fashion, resulting in arrhythmias and torsades de pointes. Patients receiving haloperidol should have their electrocardiogram monitored.

A recent retrospective study of 989 patients who were mechanically ventilated in the ICU found that those patients who received haloperidol had significantly lower mortality than those who did not (55). Although not an indication for increased use of haloperidol, the results should be reassuring to those who have concerns about its use.

Other Agents

Several anesthetic agents have been tried to sedate patients in the ICU, with unanticipated results. When nitrous oxide was used, anemia developed and led to the realization that nitrous oxide interfered with vitamin B12 metabolism. Similarly, when etomidate was used for sedation, patients developed adrenal cortical insufficiency because we now know that etomidate interferes with cortisol metabolism. However, a few anesthetic agents have withstood the test of time with respect to their use in the ICU.

Barbiturates

Barbiturates have pronounced effects on the CNS, lowering intracranial pressure and raising the seizure threshold. They have been used in the past to induce a “barbiturate coma” in patients with increased intracranial pressure and terminate seizures. Barbiturates administered by intravenous bolus produce hypotension and because of their lipid solubility, if given by continuous infusion, accumulate in fat stores and, therefore, have a duration of action that can be significantly long, i.e., days to weeks. In current practice, they are infrequently administered by continuous infusion for long-term use.

Ketamine

Ketamine is a phencyclidine derivative that is a nonbarbiturate, rapid-acting, general anesthetic that is administered parenterally to induce anesthesia. Ketamine induces “dissociative anesthesia” because it interrupts association pathways of the brain before blocking sensory pathways—patients may perceive pain, but it does not bother them. However, because it is a phencyclidine derivative, 10% to 20% of adult patients may have psychologic sequelae including hallucinations. Ketamine is used as a general anesthetic because it raises cardiac output, pulse rate, and arterial and venous pressures. Ketamine maintains pharyngeal and laryngeal reflexes without suppressing respiration. Ketamine is also a bronchodilator and has been advocated as the anesthetic agent of choice in patients with reactive airways disease. Twenty to 30 years ago, it was commonly used. Because of the increasing incidence of reactive airways disease, there is renewed interest in ketamine for sedation of patients with lung disease. A 1 mg/kg bolus of ketamine can be administered, followed by an infusion of 1.0 mg/kg per hour, titrated up to 4.5 mg/kg per hour; many administer a benzodiazepine to reduce the frequency of psychologic sequelae. Ketamine is contraindicated in patients with cardiac ischemia or raised intracranial pressure.

NEUROMUSCULAR BLOCKADE

Despite what should be effective doses of anxiolytic drugs, some patients remain delirious and agitated, and a further increase in the dose of anxiolytic drugs is prescribed because of side effects. Such patients, along with those with closed-head injuries, tetanus, and ALI, may require other therapeutic modalities. If the patient is traumatically intubated, mechanically ventilated, and receiving adequate sedation, chemical paralysis with a NMBA is an option (Table 63.12).

Patients with ARDS are often difficult to ventilate and are commonly agitated, hemodynamically unstable, and have a decreased mixed venous oxygen saturation that is life threatening. Additional sedative drugs will only worsen hemodynamics, so NMBA may be the only (life-saving) alternative that have been shown to improve gas exchange (56).

**TABLE 63.12**

**INDICATIONS FOR THE MANAGEMENT OF PATIENTS WITH NEUROMUSCULAR BLOCKING AGENTS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sedative-Agent Combination</th>
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<tbody>
<tr>
<td>Closed-head injury with raised intracranial pressure</td>
<td>Tetrac 5% with Hyperventilation</td>
</tr>
<tr>
<td>Decreased SpO2 in hypermetabolic, agitated states</td>
<td>Modes of mechanical ventilation that produce agitation, which in turn interfere with ventilation/oxygenation, e.g., pressure-controlled inverse ratio ventilation, pressure-frequency ventilation.</td>
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</table>
Chapter 63: Sedation and Neuromuscular Blockade

Purpose:
To describe the process of utilizing a nerve stimulator to stimulate the ulnar nerve, usually with tactile assessment of a neuromuscular twitch, usually tactile assessment of an abducted thumb, to assess the degree of neuromuscular block.

Definitions:
Neuromuscular block: the process by which the postsynaptic acetylcholine receptor is depressed and variably response to release of acetylcholine in the neuromuscular junction cleft
Peripheral nerve stimulation: electrical stimulation, usually from 40 to 120 mA at a peripheral nerve, usually the ulnar, either at the elbow or at the wrist
Train-of-four: a specific type of nerve stimulation in which the nerve stimulator delivers an electrical stimulus to the nerve lasting 10 ms and repeated every 500 ms for a total of 4 stimuli

Equipment:
1. Peripheral nerve stimulator
2. Two electrode pads (electrocardiogram pads may be used)

Procedure:
1. Clean the area where the electrode pads will be placed with alcohol to remove any skin oils. This will reduce the resistance at the skin and decrease the amount of current needed to stimulate the nerve. If the resistance of the skin is still high, then an abrasive compound can be used to remove dead skin.
2. Place two electrodes over the ulnar nerve, usually 3 to 5 cm apart.
3. Attach electrodes to the leads, usually the positive electrode proximally.
4. Cover the fingers and abduct the thumb. Increase the amperage of the stimulator until 4 twitches of the thumb are palpated by tactile assessment. Stimuli should not be delivered more frequently than every 20 seconds. Once 4 twitches are palpated, a supramaximal stimulus can be delivered by increasing the amperage 10% to 30% over the amperage required to palpate 4 twitches.

Goals:
1. To achieve a level of train-of-four of 2 to 4. If with 3 or 4 twitches the patient either spontaneously triggers the ventilator or exhibits muscular activity that adversely affects oxygenation or airway or intracranial pressure, then increased neuromuscular block is required.
2. A train-of-four of 1 to 0 indicates that the degree of neuromuscular block is too great, and the dosage of neuromuscular blocking agent should be decreased.

**Monitoring**

Before administering NMBAs to patients, certain requirements must be met. Patients must be mechanically ventilated, sedated, and monitored. Obviously, if patients are going to be paralyzed, they must be mechanically ventilated. Similarly, they must be sufficiently sedated that they will have no recall of the experience; most patients who are not adequately sedated will have terrifying dreams/recall (57). Most practitioners will first implement sedation therapy to the point that the patient is unconscious before initiating NMBAs therapy. Finally, the use of NMBAs is associated with many adverse side effects. Monitoring the depth of blockade and the necessity of blockade is essential in minimizing these side effects.

Assessing the degree of blockade by measuring the amount of block of the neuromuscular receptor with a twitch monitor is the preferred technique. An electrical stimulus is applied to a peripheral motor nerve, and the effects of the stimulus on the motor group supplied by that nerve are observed (Fig. 63.1).


Normal train-of-four Desired

**FIGURE 63.2. Train-of-four monitoring.** A: With the twitch stimulator at 40 to 10 mA, four twitches are measured. B: As the neumomuscular blocking agent (NMBA) takes effect, the second, third, and fourth twitches are weaker/tired. C: The goal with additional time or drug is to have one to two twitches.
Complications of NMBA

One of the most feared complications of neuromuscular block is accidental extubation. Should a paralyzed patient become accidentally extubated, time is of the essence, especially in patients with ARDS. Ventilation must begin immediately with a mask and anesthesia bag using 100% oxygen while steps are taken to reintubate the patient. Another feared complication is profound weakness once the drug is discontinued. This may seem counterintuitive—the NMBA is administered to produce profound weakness. This is true, but when the NMBA is discontinued, we anticipate that the patient will recover normal neuromuscular function within hours. One study of two of the longest-lasting NMABs (pancuronium and doxacurium) in which 40 critically ill patients were paralyzed observed that two out of three days found that once doxacurium was discontinued, patients recovered their strength within 4 hours; the patients receiving pancuronium recovered their strength within 24 hours (58).

Though not seen in this study, approximately 10% of patients who receive NMABs will develop a myopathy from which it takes days or weeks to recover (59). Weakness is a common problem in the ICU and, when secondary to muscle weakness per se, is known as CIM (critical illness myopathy). The cause of CIM in the ICU is multifactorial (60), but most studies indicate that prolonged use of NMABs in the ICU is one of the causative factors (59). Because corticosteroids are also known to produce myopathy, many intensivists are very cautious when infusing NMABs in patients who are also receiving corticosteroids (61), a common scenario. Caution is also warranted when infusing NMABs in patients who are critically ill. Daily assessments must be made to determine if NMBA use is justified, and the TOF should be maintained at one to two twitches.

TREATMENT

Aminosteroidal Compounds (Fig. 63.3)

Pancuronium

Pancuronium is a long-acting, nondepolarizing aminosteroidal compound that produces effective block for up to 90 minutes after a bolus dose of 0.06 to 0.08 mg/kg. Intermittent boluses are often administered, but it can be used as a continuous infusion, titrating the dose to one or two twitches by TOF monitor. Pancuronium induces vagolysis, limiting its use in patients who cannot tolerate an increase in heart rate. In patients with renal or liver failure, pancuronium’s effects are prolonged because of the increased elimination half-life of pancuronium and its 3-hydroxypancuronium metabolite, which has one third to one half the activity of pancuronium.

Vecuronium

With the deletion of the methyl group at one of pancuronium’s two N-methylpiperidine moieties (leaving vecuronium with a single [monouquaternary] piperidine group at the R-2 position), scientists were able to produce an intermediate-acting NMBA without the vagolytic properties of pancuronium. An intravenous bolus dose of 0.08 to 0.10 mg/kg produces block within 2½ to 3 minutes that typically lasts 35 to 45 minutes. After a bolus dose, it can be given as a continuous infusion of 0.8 to 1.4 μg/kg per minute, titrating the rate to the degree of block desired. The 3-desacetylvacuronium metabolite has 50% of the pharmacologic activity of the parent compound (62) so that patients with hepatic dysfunction may have increased plasma concentrations of both the parent compound and the active metabolite, causing prolonged block. Renal dysfunction also prolongs the duration of block. Vecuronium is associated with CIM, especially in patients receiving corticosteroids. Vecuronium is being used with decreased frequency in ICU patients.

Rocuronium

Rocuronium is a newer aminosteroidal NMBA, with an intermediate duration of action and a rapid onset that has been tested in the ICU (63). When given as a bolus of 0.6 to 0.1 mg/kg, block is almost always achieved within 2 minutes, with maximum block occurring within 3 minutes; continuous infusions are administered at 8 to 10 μg/kg per minute (64) and usually produce a fairly dense block. Rocuronium’s metabolite, 17-desacetylrocuronium, has approximately only 5% to 10% activity compared to the parent compound. Renal failure should not have an effect on duration of action, but hepatic failure may prolong rocuronium’s duration of action.

Benzylisoquinolinium Compounds

Atracurium

Atracurium is an intermediate-acting NMBA with minimal cardiovascular side effects but is associated with histamine release at higher doses. Atracurium has a unique metabolism (ester hydrolysis and Hofmann elimination) so that renal or hepatic dysfunction does not affect its duration of block. Atracurium has been associated with persistent neuromuscular weakness as has been reported with other NMABs.

Cisatracurium

Cisatracurium, one of atracurium’s 16 isomers, is an intermediate-acting benzylisoquinolinium NMBA that is increasingly used in lieu of atracurium. It produces few, if any, cardiovascular effects and has fewer tendencies to produce mast cell degranulation than does atracurium. Bolus doses with a 0.10 to 0.2 mg/kg result in paralysis in an average of 2.5 minutes, and recovery begins at approximately 2½ minutes; maintenance infusion rates should be started at 2.5 to 3.0 μg/kg per minute. Cisatracurium is also metabolized by ester hydrolysis and Hofmann elimination, so duration of block should not be affected by MODS. There have not yet been reports of significantly prolonged recovery associated with cisatracurium. The mean peak plasma laudanosine concentrations are lower in patients receiving cisatracurium compared to patients receiving clinically equivalent doses of atracurium. Laudanosine at high doses produces seizures in animals; a case of seizures in a human receiving atracurium or cisatracurium has not been reported.
Chapter 63: Sedation and Neuromuscular Blockade

Aminosteroidal Compounds

Benzylisoquinolinium Compound

FIGURE 63.3. Chemical structures of neuromuscular blocking agents. Cisatracurium is the 1R-cis 1′R-cis isomer, one of the 10 isomers found in atracurium.

RECOVERY

Patients receiving an NMBA should have daily drug holidays. If the NMBA is no longer required, it is discontinued. It is anticipated that with all the NMBAs, the TOF should normalize (four twitches) within 3 to 4 hours. If not, the patient may have a CIM associated with the NMBA (with an increased incidence in patients receiving corticosteroids and patients with sepsis, etc.). If, after 24 hours, the patient has inadequate strength, additional studies should be done to include an assessment of the antibiotics the patient is receiving, electrolytes (calcium, magnesium, phosphorus), and temperature (hypothermia prolongs neuromuscular block). If no co-morbid condition accounts for the degree of neuromuscular block, a neurology consult should be considered. In this context, an electromyography is typically performed (to rule out critical illness polyneuropathy) and, in some circumstances, a muscle biopsy is obtained. Patients with CIM secondary to the neuromuscular blockade will have loss of myosin. Treatment is supportive with maintenance of sedation, mechanical ventilation, physical therapy, skin care, eye care, and so on.

SUMMARY

Over the past 30 years, there is increased recognition that patients in the ICU are anxious, and as patients become older, have more comorbid conditions, and are more critically ill, they will increasingly exhibit agitation and delirium. These factors increase morbidity and mortality, prolonging the length of stay and worsening the outcome. Even patients who survive have memories that are disturbing and, in some circumstances, lead to the equivalent of a posttraumatic stress syndrome. Practitioners in an ICU must recognize when their patients become anxious, agitated, and delirious; identify contributing factors; and treat the disorders with anxiolytic medications. The effects of therapy must be monitored with the use of a standard scale, one that is used throughout the institution’s ICUs. In some patients in whom the sedation is inadequate, NMBAs may be indicated. Appropriate sedation, monitoring, securing of the
airway, and monitoring the adequacy of mechanical ventilation must be ensured. Patients receiving any of these medications are at risk for side effects, which must be monitored as well. An effective sedation and paralysis protocol will improve patient outcome and patient satisfaction.

**Stress Points**

1. Anxiety and pain are different emotional states, and most patients who are oriented can differentiate between anxiety and pain.
2. Before relying on pharmacologic interventions to treat pain or anxiety, first try non-pharmacologic confounding factors such as a distressed bladder in a patient who does not have a Foley catheter; hypercapnia in someone with impending respiratory failure; or someone who is becoming septic, which is manifested by encephalopathy.
3. Anxiety can lead to agitation, which in turn can result in self-injury and injury to care providers.
4. Delirium is an increasingly recognized problem in the intensive care unit (ICU), which can result in long-term cognitive impairment.
5. Physiologic derangements must first be ruled out before treating anxiety, agitation, or delirium.
6. Opioids and benzodiazepines are the pharmacologic mainstays of treating anxiety.
7. Midazolam, propofol, or dexmedetomidine are the preferred short-term (24–48 hours) treatments of anxiety.
8. Lorazepam and fentanyl are the preferred long-term anxiolytic agents.
9. Haloperidol is an effective therapy for older patients with delirium.
10. Mechanically ventilated patients who remain agitated despite adequate anxiolytic therapy are candidates for an NMBA.
11. Patients must be adequately sedated before an NMBA is administered.
12. Patients receiving NMBA must be mechanically ventilated with precautions taken to ensure that the tracheal tube or tracheostomy tube is protected.
13. The primary NMBA used for mechanically ventilated patients are the aminosteroidal compounds (pancuronium or rocuronium) and the benzylisoquinolinium compounds (atracurium or cisatracurium).
14. Daily drug “holidays” should be implemented when using anxiolytic drugs or NMBA.
15. Patients who have received anxiolytic drugs for greater than 3 to 7 days are at risk of becoming dependent and may exhibit signs of withdrawal when the drug(s) is/are discontinued.
16. Patients who have received NMBA for greater than 12 to 24 hours are at increased risk of developing critical illness myopathy (CIM) when the NMBA is discontinued.

**References**

The care of critically ill patients usually focuses on the immediate concerns of cardiopulmonary resuscitation, ventilatory support, maintenance of adequate hemodynamic parameters, and antibiotics to control infectious processes. Despite the increase in metabolic substrate utilization, as critically ill patients become catabolic, nutritional support is frequently overlooked. The extreme catabolism and negative nitrogen balance from critical illness has been well recognized for decades, as described in a 1976 review by Cuthbertson [1], but there still exists a conventional wisdom that starvation is not harmful to critically ill patients and no attempts to reverse it with nutrition support should be undertaken [1]. However, there is no medical evidence that starvation is therapeutic. In fact, Kinney [2] pointed out more than 25 years ago that the catabolic response to multiple injuries resulted in loss of up to 20% of normal body weight within 3 weeks despite some oral intake started during the first week. Kinney also noted the catabolic melting (rapid wasting) of large weight-bearing muscle groups in response to multiple injuries resulted in loss of up to 20% of normal body weight within 3 weeks despite some oral intake started during the first week. Kinney also noted the catabolic melting (rapid wasting) of large weight-bearing muscle groups.

**Chapter 64: Nutritional Issues**

**IMMEDIATE CONCERNS**

The care of critically ill patients usually focuses on the immediate concerns of cardiopulmonary resuscitation, ventilatory support, maintenance of adequate hemodynamic parameters, and antibiotics to control infectious processes. Despite the increase in metabolic substrate utilization, as critically ill patients become catabolic, nutritional support is frequently overlooked. The extreme catabolism and negative nitrogen balance from critical illness has been well recognized for decades, as described in a 1976 review by Cuthbertson [1], but there still exists a conventional wisdom that starvation is not harmful to critically ill patients and no attempts to reverse it with nutrition support should be undertaken [1]. However, there is no medical evidence that starvation is therapeutic. In fact, Kinney [2] pointed out more than 25 years ago that the catabolic response to multiple injuries resulted in loss of up to 20% of normal body weight within 3 weeks despite some oral intake started during the first week. Kinney also noted the catabolic melting (rapid wasting) of large weight-bearing muscle groups in response to multiple injuries resulted in loss of up to 20% of normal body weight within 3 weeks despite some oral intake started during the first week. Kinney also noted the catabolic melting (rapid wasting) of large weight-bearing muscle groups.
marked reduction in metabolic rate, termed the ebb phase, conjuring up an image of the patient's life ebbing away like the receding tide. The flow phase suggests the image of the returning tide, which involves the patient mounting a compensatory response to shock and tissue injury.

Further refinement of this concept has described an early catabolic period of the flow phase when muscle protein is mobilized to provide energy and substrate for tissue repair (4). This is followed in the late flow phase, a period of anabolic activity and a tissue healing component of the flow phase. Both subintervals of the flow phase increase the patient's need for nutritional supplementation to optimize healing and reduce the length of the critical illness. The flow phase is associated with an increased metabolic rate as measured by oxygen consumption/heat production, which gradually returns to normal (Table 64.1). Nutritional support prescriptions need to change throughout the patient’s period of critical illness to provide adequate protein-energy substrates during the flow phase and to prevent overfeeding when the patient’s convalescence is complete. Although critical illness most frequently compromises a patient’s ability to normally intake adequate nutrition, critical care technology offers several alternative routes of providing nutritional support. These routes of nutrition support include intravenous routes—total parenteral nutrition (TPN) and peripheral parenteral nutrition—and enteral routes with various formulae tailored to the patient’s unique requirements (Table 64.2).

### NUTRITIONAL SUPPORT SERVICE

A nutritional support service aids those caring for critically ill patients in providing appropriate nutritional prescriptions. The nutritional support service is also responsible for evaluating the patients’ responses to nutrition prescriptions. These monitored evaluations range from the patients’ actual calorie expenditure to protein requirements so as to prevent catabolism with profoundly negative nitrogen balance. Finally, the nutritional support service should be a focus for research concerning the improvement of nutritional care of critically ill patients.

Classically, the nutritional support service consisted of a registered dietitian (RD) with advanced training in the biochemical aspects of critical illness, a physician consultant, and assistants who provide nutritional consultations to metabolically unstable patients (Table 64.3). One of the team’s duties is screening patients for risks of malnutrition and diagnosing various nutritional deficiency states. The team consults on patients either by specific request or on a systematic protocol-driven basis—such as for patients in the critical care unit—according to local hospital policy.

The nutritional consult includes estimates of the patient’s metabolic rate and calorie expenditure, estimated either with the Harris-Benedict equation or actually measured via indirect calorimetry. The nutritional support team collaborates with respiratory care professionals to perform indirect calorimetry measurements.

Protein requirements are estimated from the patient’s critical illness diagnosis and monitored via visceral protein analysis or 24-hour nitrogen-balance measurements. The nutritional support team consults on patients with respiratory care professionals to perform indirect calorimetry measurements.

### Table 64.1

<table>
<thead>
<tr>
<th>Ebb</th>
<th>Catabolic flow</th>
<th>Anabolic flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂ consumption</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Nitrogen balance</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑↑</td>
<td>↔</td>
</tr>
<tr>
<td>Insulin</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Glucose</td>
<td>↑↑</td>
<td>↔</td>
</tr>
</tbody>
</table>

### Table 64.2

<table>
<thead>
<tr>
<th>COMMONLY USED ROUTES OF NUTRITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral</strong></td>
</tr>
<tr>
<td>ADVANTAGES</td>
</tr>
<tr>
<td>DISADVANTAGES</td>
</tr>
</tbody>
</table>

NPO, nothing by mouth.
CHAPTER 64: Nutritional Issues

TABLE 64.3
ORGANIZATION OF A NUTRITION SUPPORT SERVICE

<table>
<thead>
<tr>
<th>OPTIMAL ORGANIZATION</th>
<th>PRAGMATIC ORGANIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician</strong>: Provides consults for nutrition support; needs critical care experience.</td>
<td><strong>Nutritionist</strong>: Expert in critical care nutrition support dedicated to nutrition support service.</td>
</tr>
<tr>
<td><strong>Nurse</strong>: Expertise in managing tubes, i.v. catheters, and delivery of nutrition support to patients.</td>
<td><strong>Physician consultant</strong>: Intensivist overseeing care of the patients, writes orders to follow up nutrition recommendations.</td>
</tr>
<tr>
<td><strong>Pharmacist</strong>: Expertise in compounding and mixtures for nutrition support.</td>
<td><strong>Respiratory therapist consultant</strong>: Performs indirect calorimetry.</td>
</tr>
<tr>
<td><strong>Nutritionist</strong>: Expert in nutritional needs.</td>
<td><strong>Respiratory therapist</strong>: Performs indirect calorimetry.</td>
</tr>
<tr>
<td><strong>Respiratory therapist</strong>: Performs indirect calorimetry.</td>
<td>PRAGMATIC ORGANIZATION</td>
</tr>
</tbody>
</table>

Alternatives to Nutrition Support Services

The author (JKS) has participated as a physician member of a nutrition support service that rounded on all patients receiving artificial nutrition support, both parenteral and enteral, and participated in the redesigning of the service when physician shortages precluded using a dedicated physician. Currently, the author’s institution uses a RD with an advanced degree and extensive critical care experience to oversee a team of RDs who see patients by request and estimate nutritional needs. The team works with the physicians in the various critical care units to provide recommended nutritional prescriptions.

The nutritional support service also provides an educational service to critical care physicians in training, advises attending critical care physicians on nutritional issues, and spearheads nutritional research projects in the various intensive care units (ICUs). This service appears to work as well as the service organized with an obligatory physician consultant and is more cost effective in terms of physician time.

NUTRITIONAL ASSESSMENT

Critically ill patients are at risk for nutritional deficiencies. The diagnostic criteria for various protein and calorie-deficient states are noted in Table 64.4. It is wise for critical care practitioners to remember that kwashiorkor can be seen in the critically ill patient following prolonged fasting, not just in famine-stricken developing countries.

In general, protein-energy malnutrition, commonly known as protein-calorie malnutrition (PCM), has been classified as marasmus, kwashiorkor, and marasmic kwashiorkor (5). The differentiation has been the presence of edema and severe serum protein depletion in kwashiorkor as compared with body wasting without edema and preservation of plasma proteins in marasmus. Marasmic kwashiorkor exhibits features of both severe wasting (marasmus) and protein depletion with edema (kwashiorkor). Typically, marasmic kwashiorkor occurs when a chronically malnourished patient is subjected to added catabolic stress such as trauma or sepsis.

Because of the risk that a critically ill patient with underlying nutritional deficiency will develop marasmic kwashiorkor, they are screened for chronic undernutrition on admission to the hospital/intensive care unit. One such screening tool, the Malnutrition Universal Screening Tool (MUST), provides a numerical index: 0, minimal risk; 1, medium risk; or 2, high risk of malnutrition (6). The urgency of instituting nutritional support increases for patients with a score of 1 and especially 2. The MUST evaluates patients’ body mass index (weight in kilograms divided by height in meters squared [m²]), prehospital involuntary weight loss as a percent of body weight, and the potential for critical illness-induced starvation for the next 5 days.

TABLE 64.4
INDICES OF MALNUTRITION: PROTEIN-ENERGY MALNUTRITION

<table>
<thead>
<tr>
<th>% IBW</th>
<th>Undernutrition 80%</th>
<th>Marasmus less than 60%</th>
<th>Kwashiorkor 60%–80% with edema</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>18.5–20</td>
<td>Less than 18.5</td>
<td>Less than 18.5</td>
<td>Greater than 30</td>
</tr>
<tr>
<td></td>
<td>5%–10%</td>
<td></td>
<td></td>
<td>Less than 5%</td>
</tr>
<tr>
<td></td>
<td>Unplanned weight loss past 3–6 mo</td>
<td>Acute disease effect</td>
<td>Prolonged underfeeding with catabolic illness</td>
<td>Severe protein-energy deprivation, usually prolonged fasting with catabolic diseases</td>
</tr>
<tr>
<td>Arm circ. (cm)</td>
<td>23.3</td>
<td>Less than 23.5</td>
<td>Less than 23.5</td>
<td>32.0</td>
</tr>
<tr>
<td>MUST score</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>Cause</td>
<td>Low nutrition intake, chronic illness</td>
<td>Low protein calorie intake</td>
<td>Excess energy intake</td>
</tr>
<tr>
<td>T-lymphocyte count (cells/μL)</td>
<td>Less than 1,800</td>
<td>Less than 800</td>
<td>Less than 800</td>
<td>More than 2,000</td>
</tr>
</tbody>
</table>

IBW, ideal body weight; BMI, body mass index; circ., circumference; MUST, Malnutrition Universal Screening Tool.
Anthropometric indices such as MUST are useful for identifying patients who need aggressive nutritional support. However, a more precise diagnosis of a critically ill patient’s current nutritional state as well as a tool to monitor the patient’s response to nutritional support requires a combination of anthropometric, serum chemical analysis, and physiologic measurements (7). Charting the patient’s daily weight is one of the simplest anthropometric measurements that can identify both long-term loss of lean body mass and the development of edema. The body mass index, mid-upper arm circumference, and estimate of body fat from triceps skin fold are other measurements to track the critically ill patient’s nutritional state (7).

Many biochemical markers are available to track a patient’s nutritional status. These include albumin concentration, estimates of whole body potassium, water balance, and visceral proteins such as prealbumin, transferrin, and retinol-binding protein. Albumin concentration is a good prognostic marker of a patient’s chronic nutritional state. Perioperative mortality has been shown to increase when albumin concentration is less than 30 g/L (8). However, serum albumin has a long serum half-life and, hence, does not reflect acute responses to nutritional therapy.

Total body potassium represents lean cellular mass and can be a useful measurement of changes in lean tissue mass that occur rather slowly. In a similar fashion, 24-hour creatinine production is a marker of total skeletal muscle mass. However, both of these markers change relatively slowly and may not be useful to monitor the patient’s response to nutritional therapy for critical illness.

Visceral proteins—prealbumin, transferrin, and retinol-binding protein—with their short half-lives, can be useful to monitor protein synthetic response to nutritional support therapy (7). Measuring nitrogen (N) balance via a 24-hour urine urea nitrogen excretion is a very useful technique to monitor response to nutritional support. Nitrogen balance, defined as protein intake minus protein N excretion, is approximately zero (balanced) in the healthy, free-living state. The catabolism triggered by critical illness will lead to increased loss of protein N and a negative nitrogen balance. The goal of the intensivist is to provide nutritional support to lead to a positive N balance until the patient’s depleted protein state is replenished.

The most direct method to monitor N balance is to measure 24-hour protein intake, divide the number by 6.25, which is the average ratio of molecular weight of amino acid to nitrogen content, then subtract protein loss, represented by the excretion of urea nitrogen N (UUN) over the same 24-hour period. Usually, an empiric constant of 4 gm N per day is added to the UUN measurement to account for nonurinary losses of protein (Table 64.5). If the patient’s blood urea nitrogen (BUN) is not stable, corrections for retained N must be performed (Table 64.5).

Energy expenditure may be calculated by the Harris-Benedict equation or measured directly with an indirect calorimeter. The Harris-Benedict equation is fairly accurate if the patient’s weight is near his or her ideal body weight. Because lipid has a metabolic rate different from lean body, the Harris-Benedict equation may not accurately estimate the patient’s actual caloric expenditure, especially in the obese.

Indirect calorimetry takes advantage of the fact that oxygen consumption (VO₂) and carbon dioxide production (VCO₂) are stoichiometric products of aerobic metabolism. Thus, the patient’s pulmonary gas exchange is measured over a several-hour period and converted to the patient’s actual energy expenditure by empiric equation (9) (Table 64.6). The longer the time period over which the measurements occur, the closer to the patient’s actual average daily metabolic rate. Because patients have a diurnal variation, as well as an activity variation, in metabolic rate, short time periods of indirect calorimetry may overestimate or underestimate the average 24-hour energy expenditure. Indirect calorimetry also provides information that is useful for managing a patient’s respiratory status, because a high oxygen consumption and carbon dioxide production is associated with obligatory mechanical ventilatory support. Furthermore, mean expired carbon dioxide, a value required for accurate measurement of pulmonary dead space, is directly measured by indirect calorimetry.

### Table 64.5

<table>
<thead>
<tr>
<th>Nitrogen intake</th>
<th>Protein administered in g/day divided by</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (assumed to be 0)</td>
<td>Y X 0.16 = (B) in g</td>
</tr>
<tr>
<td>1) 24-h urine urea N in g/day =</td>
<td>(A) in g</td>
</tr>
<tr>
<td>2) Measure of proteinuria, if any =</td>
<td>Y</td>
</tr>
<tr>
<td>3) Correction for any rise of BUN assuming no change in body weight in kg =</td>
<td>Z in g L⁻¹</td>
</tr>
<tr>
<td>Rise in blood urea (in 24 h) =</td>
<td>Z in g</td>
</tr>
<tr>
<td>Z in g x 60% body weight = 2860 = Z x body weight</td>
<td>x 0.28 = (C) in g</td>
</tr>
<tr>
<td>N balance = (nitrogen intake – nitrogen loss)</td>
<td></td>
</tr>
</tbody>
</table>

*28 is mol weight of N in urea and 60 is total mol weight of urea, i.e., 1 g urea = 0.16 g N.*

### Table 64.6

<table>
<thead>
<tr>
<th>Indirect Calorimetry—Daily Energy Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>kcal/day = 3.9 × VO₂ (L/24 h) × 2.17 × VCO₂ (L/24 h)</td>
</tr>
<tr>
<td>VO₂ = ([F₄CO₂ × Vl] – [F₆CO₂ × Vl]) x 1,440 min/24 hrs</td>
</tr>
<tr>
<td>VCO₂ = F₆CO₂ × Vl – F₄CO₂ × Vl</td>
</tr>
<tr>
<td>Vl = (1 – F₆O₂) – F₄CO₂</td>
</tr>
<tr>
<td>VO₂ = oxygen consumption (L/24 h)</td>
</tr>
<tr>
<td>VCO₂ = carbon dioxide production (L/24 h)</td>
</tr>
<tr>
<td>Vl = inspired ventilation (L/min)</td>
</tr>
<tr>
<td>F₆O₂ = mole fraction inspired oxygen</td>
</tr>
<tr>
<td>F₆CO₂ = mole fraction expired oxygen</td>
</tr>
<tr>
<td>F₄CO₂ = mole fraction expired carbon dioxide</td>
</tr>
<tr>
<td>(assumed to be 0)</td>
</tr>
<tr>
<td>F₄CO₂ = mole fraction inspired carbon dioxide</td>
</tr>
<tr>
<td>UN = 24-hour urinary nitrogen loss (g/24 h)</td>
</tr>
</tbody>
</table>
Overall, monitoring of a patient's response to nutrition support is performed by a battery of the tests described above. Daily weights are tracked to monitor a patient's response to nutritional support. Initially, weight gain will represent an increase in total body water, which will start decreasing (dilution) as the patient becomes anabolic. During the anabolic phase, the patient will initially lose weight via diuresis of water, then gain weight as lean body mass. Obese patients may continue to lose weight from fat stores if they are fed a high-protein, restricted calorie diet. Repeated indirect calorimetry can follow the respiratory quotient (VCO₂/VO₂) that provides a measure of whether a patient is being underfed or overfed. Utilization of protein intake can be tracked by repeated 24-hour N balances via urine urea nitrogen measurements and nutrition intake.

Beyond direct physiologic measurements of adequacy of nutritional intake, functional measurements that indirectly depend on the nutrition response, such as immunologic function, can be followed. The severely malnourished patient exhibits immunosuppression by skin test anergy, low absolute lymphocyte count, low T-cell lymphocyte count, difficulty mounting an immune response, and an increased susceptibility to infections; these functions should improve with aggressive nutritional support.

**TIMING OF NUTRITIONAL SUPPORT**

Nutritional evaluation of the critically ill frequently reveals patients admitted to the ICU who exhibit signs of marasmic kwashiorkor and who have an urgent need for nutritional support. Once the decision is made to provide nutritional support for the critically ill, one has to decide on the best route of administration—parenteral or enteral. Data from one to two decades ago suggested that parenteral nutrition (total parenteral nutrition or TPN) was associated with a higher mortality rate than enteral nutrition (total enteral nutrition or TEN) in patients who had abdominal trauma (10,11). However, more recent studies in other patient populations have failed to confirm these results (12,13). In several studies comparing the administration routes of nutritional support, the major difference between TEN and TPN was the fact that enteral-fed patients had more frequent interruptions of nutrition (14,15). Therefore, TEN patients received somewhat less nutritional substrate than TPN patients.

Historically, there has been grave concern that TPN puts patients at risk for serious infection complications. However, recent studies reveal that bloodstream infections are relatively rare during TPN, and TEN patients have a significantly higher incidence of feeding tube complications than TPN patients have from central venous catheter complications.

In one review of infectious complications in the ICU, it was noted that inadequate nutritional intake—less than 7 kcal/kg per day—was associated with sepsis. In this group of underfed patients, those who received TEN were equally likely to have infectious complications as those who received TPN (16). This study supports the practice of starting early and adequate nutrition support to prevent infectious morbidity.

One of the alleged benefits of early enteral feeding is to maintain the integrity of the gut mucosal lining and thus limit translocation of microorganisms from intestinal lumen to bloodstream. This hypothesis was tested using a macromolecular marker of gut permeability in two groups of patients: those with early enteral feedings and those kept NPO (nothing by mouth) (17). There was no demonstrated difference in permeability between the two groups, which suggests that bacterial translocation from the gut to the bloodstream is not the source of bloodstream infections in patients who are fed parenterally.

TEN does have some demonstrated advantages over TPN, including lower cost, using gut absorption to regulate total body water balance, and the ability to utilize larger molecules as a food source. TPN has advantages over TEN that include fewer interruptions for NPO status prior to procedures and no interference with drug absorption.

We recommend that patients receive early nutritional support to help reduce infectious complications. Because patients need adequate protein and calorie intake to prevent complications from infections, those patients who cannot tolerate TEN should be immediately switched to TPN. It is clearly an error to withhold TPN for the notion that the risks of TPN outweigh the risks of starvation for several days.

The marked improvement in managing central venous access that developed in recent years has markedly reduced the risk of infectious complications of TPN. Furthermore, accurate and widespread assessment of actual metabolic needs with indirect calorimetry and N balance has led to a significant reduction in TPN calorie load that has decreased metabolic complications of TPN (18,19).

**NUTRITION SUPPORT FOR SPECIFIC ORGAN DYSFUNCTION**

Nutritional support is often modified for specific organ dysfunction because certain pathophysiologic conditions lead to changes in the metabolic handling of nutrient substrates. These disease states include liver failure, kidney failure, diabetes/glycemic control, and brain injury.

**Hepatic Failure**

Liver failure is one of the most vexing morbidities requiring prescriptions for nutritional support. In severe hepatic failure, nitrogen from amino acid metabolism remains as ammonia because it is not metabolized to urea. Hyperammonemia leads to secondary neurologic dysfunction including hepatic coma. Thus, protein needs to be administered in amounts to replace catabolic losses, but not high enough to lead to high levels of ammonia. Sorbitol may be administered enterally to try to lower ammonia by increasing gut motility and decreasing intestinal transit time to decrease the absorption of proteins and ammonia from bacterial metabolism of intraluminal amino acids. However, sorbitol has no effect on hepatic amino acid metabolism.

Hepatic glycerogen stores are also depleted in end-stage hepatic failure, making the maintenance of normoglycemia extremely difficult. High glucose feedings may be required to compensate for lack of hepatic glucose production. The bottom line in end-stage hepatic failure is that nutritional support needs to be modified to minimize plasma ammonia levels and maintain normal glucose levels; nutritional support will not, of course, reverse significant hepatic injury.
Renal Failure

Rising blood levels of the nitrogenous waste product urea and creatinine are the hallmarks of renal failure. Acute renal failure is, unfortunately, rather common in critically ill patients in response to intrarenal insults from circulating inflammatory mediators as well as changes in renal perfusion. Although past nutritional efforts for acute renal failure have focused on limiting protein intake to reduce urea production or using only essential amino acids to recycle amino acids to reduce urea production, modern critical care uses renal replacement therapy (20,21). Either hemodialysis or continuous venovenous hemofiltration is used to maintain acceptable levels of urea, creatinine, and electrolytes until the kidney regains its function. One of the few evidence-based therapies that enhances the repair of acute renal failure is nutritional support with adequate protein for renal healing. Thus, efforts to restrict protein intake in patients with acute renal failure are misguided and should be discouraged. Renal replacement therapy should be instituted to maintain acceptable levels of urea while the healing kidney is supported by adequate protein replacement. Prior to the commencement of renal replacement therapy, serum electrolytes need to be carefully monitored because renal failure often leads to excess water (H₂O), low sodium (Na), and high potassium (K). Nutrition support may have to be modified to correct serum electrolyte disorders.

Glycemic Control

Hyperglycemia is a common occurrence in critically ill patients. Not all hyperglycemic critically ill patients have diabetes, but the hormonal milieu of the stress response tends to cause hyperglycemia. Among the hormones that increase plasma glucose are growth hormone, cortisol, glucagon, and epinephrine (22). Furthermore, one of the diagnostic hallmarks of sepsis is glucose intolerance/insulin resistance. Some authors have postulated that hyperglycemia has survival advantages in providing energy substrate for collagen synthesis for wound healing. A large randomized trial compared glucose levels of 180 to 200 mg/dL in the control group, consistent with the survival advantage hypothesis, to normoglycemia of 80 to 110 mg/dL in the experimental group (23). The normoglycemic group had a significant improvement in outcome effects that persisted for several months post recovery. These effects included decreased ICU length of stay, reduced infectious complications, and survival. Despite fears that tight glucose control might expose patients to risks of dangerous hypoglycemic episodes, it is recommended that critically ill patients be managed with normal glucose levels (23,24). Furthermore, in the controlled environment of the critical care unit, where it is feasible to monitor glucose levels every hour, an insulin infusion is the best method to manage glucose concentrations. Infusions of regular insulin can be rapidly changed to respond to hourly, or more frequent, bedside glucometer measurements that may vary widely in unstable critically ill patients. To protect patients from hypoglycemia from the insulin infusion, patients receive either nutritional support (TPN or TEN at goals) or, if needed, a 10% dextrose infusion (23–25).

Brain Injury

The injured brain is characterized by an impairment of the blood-brain barrier, which causes increased susceptibility to changes in plasma concentrations of glucose and electrolytes. The prevention of edema in the injured brain, an essential requirement to allow the brain to heal and reorganize neural pathways, places demands on the composition of nutritional support. Nutritional goals for the head-injured patient include avoidance of hyperglycemia, hyperosmolar state, and maintenance of normal sodium and potassium. Hyperosmolar coma, a known complication of TPN, is usually caused by extreme hyperglycemia and can be treated with insulin. This is certainly another good reason to accurately assess a patient’s metabolic rate and calorie requirement from nutrition support. Hyperglycemia, even with normal osmolality, is detrimental to the injured brain by causing cerebral edema in ischemic areas of the brain. This occurs when one glucose molecule diffuses into the brain and is anaerobically metabolized to two lactic acid molecules that are highly polar and do not diffuse out into the bloodstream. Thus, the interior of the cell increases in osmolality (more nondiffusable particles) relative to plasma and attracts increased cell water. The above effect is magnified by hyperglycemia in patients who have brain lesions associated with low perfusion/O₂ delivery (26,27).

Besides adjusting nutritional support to maintain euglycemia, with appropriate calorie administration and insulin use, sodium replacement is important in brain-injured patients. Many patients with brain injuries develop hyponatremia, which tends to increase the risk of cerebral edema from excess plasma water and decreased serum osmolality. Cerebral salt-wasting syndrome or inability to conserve sodium in the kidney needs to be differentiated from syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH). Cerebral salt-wasting patients tend to be hypovolemic and need extra sodium replacement in their nutrition support, whereas patients with SIADH tend to be hyperosmolar and generally need fluid restriction to correct their serum sodium levels. Brain-injured patients will require adequate protein intake to compensate for their increased demands to provide brain healing. The metabolic rate should be measured directly and caloric needs met by appropriate amounts of nutritional support. There is some concern about excitatory amino acids having deleterious effects on the injured brain, but it is unclear that nutritional support affects the CNS concentration of these amino acids.

SUMMARY

Nutritional support for critically ill patients is often overlooked by clinicians concerned with the immediate concerns of hemodynamic instability and respiratory failure. However, starvation is not therapeutic, and prolonged inadequate energy intake will lead to malnutrition states in critically ill patients. Increased metabolic activity stimulated by stress hormonal response and a generalized inflammatory state may accelerate the appearance of malnutrition. Adequate protein-energy intake reduces critical care unit-acquired bloodstream infections, and aggressive insulin management to maintain euglycemia will
reduce mortality as well as infectious complications of critical illness. Supported in part by NIH GM 39277 (TCV).

References


Chapter 65: PRACTICAL ASPECTS OF NUTRITIONAL SUPPORT

CHRISTOPHER D. TAN

"If the gut works, use it. If it isn’t working, make it work.” This adage summarizes how a clinician should approach nutritional support in the intensive care unit. Although it may seem intuitive that parenteral nutrition should improve morbidity and mortality because the patient is “being fed,” conclusive data are sparse. On the contrary, much has been published on the benefits of enteral feeds, especially if the patient is fed early (1,2).

Being familiar with nutrition support is not just about calories and proteins the patient needs, but requires familiarity with the ordering, initiating, monitoring, and discontinuing processes of nutrition support as well. This chapter is meant to complement the previous chapter by taking the clinician through the practical aspects of nutritional support.

WRITING A TOTAL PARENTERAL NUTRITION ORDER

In 2003, the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) assembled a task force to look into the safe practice of parenteral nutrition practice. Out of this task force emerged the 2004 A.S.P.E.N. guidelines on Safe Practice for Parenteral Nutrition 131, as well as the 2003 A.S.P.E.N. Nutrition Support Practice Manual (2nd ed.) (4). The latter is considered to be one of the primary resources for nutritional support.

Life-threatening errors continue to occur in the preparation and delivery of parenteral nutrition (PN) admixtures to...
patients. Many of these errors are related to the ordering process. One solution to this problem is to use a standardized PN form that is institution specific. Research has demonstrated the benefit of a standardized order-writing process in reducing prescriber errors (3). These forms, however, are not perfect themselves, as shown by one study, which reported an increase in prescriber errors after a standardized PN order form was introduced (5).

Providing nutrition support to critically ill patients is a complex but important task. The ultimate goal should be to minimize loss of lean body mass, especially in patients with burns, sepsis, acute respiratory distress syndrome, and trauma. Energy expenditure of the critically ill patient depends on the underlying disease state, as well as the nutritional status of the patient before the injury or illness. Although the Harris-Benedict equation is widely used to estimate the basal energy expenditure, the stress and activity factors used to adjust for the severity of illness may be excessive, and can lead to overfeeding (4).

One recommendation from the A.S.P.E.N. guidelines, as well as from the American College of Chest Physicians (ACCP), is using a total energy requirement of 25 kcal/g/dig/day (4,6). If the patient is obese, then an adjusted body weight should be used in the calculation (4).

Protein requirements for critically ill patients with normal renal function can range from 1.3 to 2 g/kg/day (moderate to severe stress), using the preemorbid body weight or the adjusted body weight if obese (4). In patients with acute renal failure, the following amounts of protein are recommended: 0.8 to 1.2 g/kg/day if patients are not dialyzed, 1 to 1.4 g/kg/day in patients receiving dialysis, and 1.5 and 2.5 g/kg/day in patients undergoing continuous renal replacement therapy (CRRT) (4). For chronic kidney disease, the A.S.P.E.N. recommends 0.5 to 0.6 g of protein/kg/day (4). The ACCP, on the other hand, recommends no change in the amount of protein given to patients with acute renal failure versus patients with normal kidney function (i.e., 1.2-2 g/kg/day) (6).

In chronic renal failure, the ACCP recommends 0.5 to 0.8 g of protein/kg/day (6).

There are at least three different ways PN can be ordered. If the patient has only peripheral venous access, peripheral parenteral nutrition (PPN) is used. Compared to total parenteral nutrition (TPN), PPN is lower in osmolarity (<900 mOsm/L) to minimize thrombophlebitis (7). For formulas to be given via central line, TPN can be administered in two ways. One is a two-in-one TPN formula, which is protein and dextrose in one bag, with the intravenous fat emulsions (IVFEs) hung separately. The other method is a three-in-one TPN formula, in which all three fuel substrates (amino acids [AAs], dextrose, and fats) are mixed in one bag. Each has advantages and disadvantages. The two-in-one formula allows visualization of particulate matter but takes up more nursing time and requires two different intravenous lines. The three-in-one is more user friendly since only one bag needs to be hung, but the cloudiness of the solution will not allow visualization of particulate matter. The A.S.P.E.N. guidelines do not favor one formula over another.

Most institutions have premixed PN formulas with known amounts of protein (g/L) and calories (kcal/L) to make it easier for order writing. For three-in-one formulas, once the caloric and protein needs have been assessed, the volume of PN needed is calculated to match the assessed needs. For instance, if 2 L of formula X from your institution is needed to meet needs, then the PN rate should be 83 mL/hour (i.e., 2,000 mL/day ÷ 24 hours/day). If your institution does not have premixed PN formulas or none of the formulas is appropriate for your patient, then a customized mixture will be necessary. This will be discussed later in the chapter.

For two-in-one formulas, fat is administered separately, usually three times a week. To calculate the total caloric contributions, the amount of calories per week from fat is totaled and then divided by 7 days per week to obtain the calories per day. For example, Intralipid 20% 500 mL containing 1,000 kcal is given three times a week. The caloric contribution per day would be 3,000 kcal/week ÷ 7 days/week, which equals 429 kcal/day from fat. This amount is then added to the known calories provided by the dextrose and amino acids in the two-in-one formula.

Most institutions have default amounts of additives (electrolytes) to facilitate the ordering process. The amounts are based on guidelines and may not suit every patient. For example, using default additives with potassium and phosphorus in a renal failure patient can lead to hyperkalemia and hyperphosphatemia, respectively.

Ordering electrolytes and other additives is as much an art as it is a science. With practice, one can develop a “feel” for how patients will respond to the additives depending on their condition. The most difficult part of the ordering process is how much electrolyte to add initially. The subsequent adjustments are easier with adjustments to increase, decrease, or keep the additives the same, depending on the laboratory values. Table 63.1 summarizes how to determine the quantity of electrolytes to add to PN solutions.

### INITIATING PARENTERAL NUTRITION

The A.S.P.E.N. guidelines suggest no more than 150 to 200 g/day of glucose initially to ensure tolerance of PN (4). Thus, it may be prudent to infuse only 1 L of the TPN on the first day (i.e., 42 mL/hour) and reaching goal rate on day 2 or 3, depending on the patient’s tolerance of volume and macronutrients. It is imperative that central line placement be verified by radiography before initiating TPN, and that TPN be administered through a dedicated infusion port via an infusion pump that is equipped with protection from “free flow” and has reliable alarms. To reduce the chance for infusing particulates, microorganisms, and pyrogens, a 1.2-micron filter may be used (anything smaller than 1.2 micron may filter out the fat emulsions in a three-in-one formula). Alternatively, a 0.22-micron filter may be used for a two-in-one formula. PPN formula is not as caloric dense and contains less protein; therefore, it may be initiated at goal rate (assuming the patient is able to tolerate the fluid load). The PN administration set must be changed every 24 hours using aseptic techniques and universal precautions. An exception is if the PN does not contain fat emulsions (i.e., the two-in-one formulation); then the administration set may be changed every 72 hours (4).

However, the administration set used in infusing the IVFE separately must be discarded after use or at least every 12 hours (4).
The transitional period is the time during which enteral feeding is started and PN is discontinued. Patients who are young, have no history of malignancy, and were well nourished before PN was started can have their PN discontinued as soon as they are able to tolerate solid food. In general, PN can be discontinued once 60% of energy needs is met enterally (4). In older debilitated patients who have a history of malnutrition and malignancy, transitioning to enteral feeds may be more challenging. Calorie counts help to guide the reduction or discontinuation of PN. Factors such as aspiration risk, appetite, strength, and feed play a role in whether patients successfully transition to enteral feeds.

Terminating TPN is just the opposite of initiating. The major concern is rebound hypoglycemia from rapid cessation of PN. It is recommended that the TPN be decreased by half for 1 to 2 hours before discontinuation if the current infusion rate is >42 mL/hour (4). This will allow time for the body to adjust its insulin secretion to decreasing amounts of circulating dextrose and avoid hypoglycemia. Weaning of PN is not necessary in patients receiving oral nutrition.

If problems occur with the TPN bag that render it not usable (e.g., a leak in the bag) and the patient is on a rate >42 mL/hour, dextrose 10% (D10W) or dextrose 10% with 0.9% sodium chloride (D10NS) should be infused at the same rate as the TPN to avoid rebound hypoglycemia. In the same scenario, dextrose 5% (D5W) may be substituted in place of PPN, not because of rebound hypoglycemia, but more for maintaining caloric intake.

**ICYCLIC PARENTERAL NUTRITION**

PN that is infusing 24 hours a day means that the patient is tethered to the intravenous pole, limiting mobility. Getting the patient who is receiving PN to eat more may be problematic because the satiety center is constantly being stimulated. A reduced oral intake can be expected if more than 25% of caloric needs is provided by PN (9). In these two scenarios, transitioning over to cyclic PN may be a good option. Cyclic or nocturnal PN is almost like regular PN except that instead of infusing the PN over 24 hours, the same volume is infused over a shorter period (12 or 14 hours), starting in the evening and finishing in the morning. Cyclic PN allows patients to be more mobile during the day, as well as have more of an appetite. Other benefits of cyclic PN include less deterioration of liver function (10).
Before transitioning to cyclic PN, the nutritional goal needs to be defined. Full support versus supplemental to a diet. Full support means that the total amount of protein and calories will be provided. In this case, it is important to make sure that the TPN is already concentrated, since the patient will be receiving the same volume that was previously given over 24 hours for a shorter period of time. If the goal is to have the patient eat more but not get behind in nutrition, then one can provide 50% of assessed needs as cyclic PN while the patient is fed orally or enterally. An important aspect of cyclic TPN is calculating the tapered flow rate to minimize harmful fluctuations of blood sugar (i.e., hyperglycemia during initiation of PN and rebound hypoglycemia during cessation of PN). One simplified method of calculating the reducing cyclic PN rate comes from Stanford University (11):

\[ v = r + 2r(4t - 4) + 2r + r, \text{ where } t = \text{ cyclic PN time}, \]

\[ v = \text{volume infused, and } r = \text{ rate of PN} \]

\[ v = 6r + 4r - 16r \]

\[ v = 4r - 10r \]

\[ v = r(4t - 10) \]

\[ v = \frac{r}{4r(10)} \]

\[ v = 1,500 \text{ mL}/(4[12 \text{ hours}]) - 10 \]

\[ r = 39.47 \text{ or } 40 \text{ mL/hour} \]

For example, the patient will be receiving a total of 1,500 mL (10% of PN formula X over 12 hours). To calculate the cyclic TPN rate ("v"), the formula uses the model \( r \times \text{mL/hour} 	imes 1 \text{ hour} + (2r \text{mL/hour} 	imes 1 \text{ hour}) + (4r \text{mL/hour} 	imes \text{cyclic PN time} - 4) + (2r \text{mL/hour} 	imes 1 \text{ hour}) + (r \text{mL/hour} 	imes 1 \text{ hour}) \). Therefore, the cyclic TPN will be ordered as follows: 40 mL/hour \( \times 1 \text{ hour} \), then 80 mL/hour \( \times 1 \text{ hour} \), then 160 mL/hour \( \times 8 \text{ hours} \), then 80 mL/hour \( \times 1 \text{ hour} \), then 40 mL/hour \( \times 1 \text{ hour} \), then 160 mL/hour \( \times 8 \text{ hours} \), then 80 mL/hour \( \times 1 \text{ hour} \), then 40 mL/hour \( \times 1 \text{ hour} \), then stop. It is important that there be a "ramp up" and "ramp down" during cyclic TPN infusion to avoid significant glucose fluctuations. Glucose may be drawn 60 minutes after the maximal infusion rate, or 60 minutes after discontinuation of cyclic PN to make sure the patient is tolerating (4).

### HIDDEN SOURCES OF KCALS

Inadvertent hypercaloric feeding can result in increased carbon dioxide production, hyperglycemia, and hepatomegaly, all of which may be detrimental to the critically ill patient. It is important to pay attention to medications that can inadvertently lead to excessive calories. Propofol, which is suspended in 10% Intralipid, contributes 1.1 kcal/mL. A patient on a relatively high dose of 50 \( \mu \)g/kg/minute (assuming a 70-kg patient) can easily receive an extra 554 kcal/day.

Another hidden source of calories is the dextrose concentration in the dialysate fluid of patients receiving CRRT. Diffusion greatly influences dextrose absorption across the hemofilter. It has been reported that the daily caloric contribution ranges from 123 to 2,388 kcal depending on the dextrose concentration of 0.5% to 4.25% in the dialysate solution. Approximately 43% to 45% of dextrose can be absorbed by the body across the hemofilter (12). Other factors that affect the degree of dextrose absorption are the dialysate flow rate, blood flow rate, ultrafiltration rate, arterial blood glucose concentration, and integrity of the hemofilter (12-14). Using the lowest possible concentration of dextrose in the dialysate is the best way to avoid hyperglycemia.

### FLUID RESTRICTION

In institutions that use electronic admixing equipment (e.g., Baxter’s Automaiz/Micromix), formulating the TPN is virtually just a touch of a button. Reformulating PN formulas to maximize caloric density and minimize fluids is not labor intensive. Although mixing standard or nonstandard formulas makes little difference from an admixture standpoint when using the automatic mixing machines, the calculation of a nonstandard PN formula can be tedious and requires knowledge of base solution stabilities used by the pharmacy to administer the PN (see calculations below).

### ESTIMATING PROTEIN, FAT, AND CARBOHYDRATE REQUIREMENTS

As discussed earlier, most institutions will likely have premixed standard PN formulas for ease of ordering. However, there are times when the clinician has to formulate a PN formula for special cases. One instance could be if the assessed calories and proteins do not match up to any of the premixed formulas. Another instance could be if the patient has hypertriglyceridemia, and the PN formula has to be adjusted so that the fat is taken out and the dextrose is increased to compensate for the absence of fat. To better understand how to formulate a three-in-one TPN formula, a sample case will be presented.

### Base Solutions (may vary with different institutions)

- Amino acids base solution: Travanol 10%
- Dextrose base solution: 70%
- Intralipid base solution: 20%

#### STEP 1: Assess calories and volume provided by protein (4 kcal/g).

- 4 kcal/1g = x/130 g (see Table 65.2)
- x = 520 kcal (from protein)

#### STEP 2: Assess amount of nonprotein calories required. Nonprotein calories should be 15% to 30% fat based, and

<table>
<thead>
<tr>
<th>Fuel substrates</th>
<th>RQ</th>
<th>Kcal per gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fats</td>
<td>0.7</td>
<td>9 kcal/g</td>
</tr>
<tr>
<td>Intralipid 10%</td>
<td>1.1</td>
<td>1 kcal/mL</td>
</tr>
<tr>
<td>Proline 20%</td>
<td>2 kcal/mL due to the presence of phospholipids</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>1</td>
<td>3.4 kcal/g</td>
</tr>
</tbody>
</table>

#### TABLE 65.2: RESPIRATORY QUOTIENT (RQ) AND KCALORIES PER GRAM OF DIFFERENT FUEL SUBSTRATES

- Inadvertent hypercaloric feeding can result in increased carbon dioxide production, hyperglycemia, and hepatomegaly, all of which may be detrimental to the critically ill patient. It is important to pay attention to medications that can inadvertently lead to excessive calories. Propofol, which is suspended in 10% Intralipid, contributes 1.1 kcal/mL. A patient on a relatively high dose of 50 \( \mu \)g/kg/minute (assuming a 70-kg patient) can easily receive an extra 554 kcal/day.

- Another hidden source of calories is the dextrose concentration in the dialysate fluid of patients receiving CRRT. Diffusion greatly influences dextrose absorption across the hemofilter. It has been reported that the daily caloric contribution ranges from 123 to 2,388 kcal depending on the dextrose concentration of 0.5% to 4.25% in the dialysate solution. Approximately 43% to 45% of dextrose can be absorbed by the body across the hemofilter (12). Other factors that affect the degree of dextrose absorption are the dialysate flow rate, blood flow rate, ultrafiltration rate, arterial blood glucose concentration, and integrity of the hemofilter (12-14). Using the lowest possible concentration of dextrose in the dialysate is the best way to avoid hyperglycemia.
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the rest (70%–85% of nonprotein calories) should be dextrose based (4).

2. 000 kcal (total caloric needs) − 520 kcal (calories from proteins) = y
   1,480 kcal = 0.2 (i.e., 20% calories from fat)
   ∼ 300 kcal (fat calories)
   1,480 kcal − 300 kcal = 1,180 kcal (dextrose calories)

STEP 3: Assess volume contributed by dextrose (3.4 kcal/g) and fat calories, rounding up the numbers.

Fat calories: 300 kcal

Intralipid: 20% or 2 kcal/mL (see Table 65.2)
Therefore, 300 kcal = 150 mL fat volume
Since 20% is 20g/100mL, 150 mL = 30g fat

Dextrose calories: 1,180 kcal = 3.4 kcal/g = 347 g (see Table 65.2)
Dextrose 70% = 70g/100mL = 347 g/z
z = 495.7 or ~ 496 mL (volume from dextrose)

STEP 4: Add up the protein, fat, and dextrose volume to calculate minimum amount of fluid needed to make the TPN formula.

1,300 mL (from AA) + 150 mL (from fat) + 496 mL (from dextrose) = 1,946 mL
1,946 mL/day = 24 hour/day = ~ 81 mL/hour.

The 1,946 mL volume represents the minimum amount of volume needed to make the TPN (i.e., the TPN is “concentrated”).

STEP 5: Put it all together. The PN order would look something like this:
Amino acids = 130 g
Dextrose = 347 g
Fat emulsion = 30 g
Rate = 81 mL/hour (i.e., 1,946 mL over 24 hours)
This formula will provide 1,997 kcal = 130 g protein over 24 hours

If the clinician wanted 100 mL/hour of fluids, the rate can simply be changed to 100 mL/hour (i.e., 2,400 mL over 24 hours; sterile water is added to make up the balance) without affecting the amount of calories and proteins given to the patient. Since 81 mL/hour (1,946 mL) represents the minimum volume needed to make the above TPN, it is not possible to go below 81 mL/hour without decreasing the calories and proteins given to the patient.

ELECTROLYTE ABNORMALITIES

Refeeding syndrome is an imbalance of electrolytes as well as vitamins, micronutrients, and fluids that occurs within the first few days of refeeding malnourished patients as nutrients replete the intracellular space (15). The hallmark biochemical findings include hypophosphatemia (intracellular shift plus depletion of phosphorus substrate to synthesize adenosine triphosphate [ATP]), hypomagnesemia (intracellular shift plus magnesium is a cofactor in many enzymatic functions), and hypokalemia (intracellular shift of potassium with insulin secretion as a response to dextrose infusion). Patients may exhibit respiratory distress, cardiac arrhythmias, congestive heart failure, hemolytic anemia, or paresthesias, or they may die (16). The three most important steps in preventing refeeding are (a) high-risk patients (chronic alcoholism, kwashiorkor, marasmus, rapid refeeding) and those receiving high TPN rates must be identified (17); (b) baseline electrolytes must be checked before the initiation of PN (4,17), and low magnesium, phosphorus, or potassium levels must be corrected immediately; (c) the TPN rate should be advanced slowly (<110 g/day of carbohydrates) as tolerated over several days before going to the goal rate (4,17). In patients receiving enteral nutrition (EN), the rate could be advanced more aggressively if needed, provided that electrolytes are monitored closely and repleted in a timely manner (18).

Replacing electrolytes is both a science and an art, because patients respond differently. Table 65.3 will help guide the clinician in managing electrolyte imbalances that occur. There are two things to remember when adjusting the electrolytes in PN: First, the degree of metabolic derangements must be determined before any adjustments are made. Second, PN should not be used to replace electrolytes rapidly, but should be used for maintenance.

MONITORING

The potential for serious complications is high in patients receiving PN unless careful monitoring is conducted by clinicians. Furthermore, appropriate monitoring can be cost effective by avoiding complications. Suggested protocols for monitoring PN in adults are shown in Table 65.4.

WRITE ENTERAL ORDERS

Ordering enteral feedings is less complex than ordering PN, but it could be just as confusing with many different formulas. Enteral feeding should be started as early as possible since it is a “pharmacotherapy” for the gut (improves mesenteric blood flow and maintains gut integrity). Feeding early, which is defined as 48 hours within mechanical ventilation onset, is associated with a 20% decrease in intensive care unit (ICU) mortality and a 25% decrease in hospital mortality, according to a recent retrospective, multi-institutional study looking at 4,409 patients (1). When choosing enteral formulas, consideration depends on the patient's digestive capability, fluid restriction status, electrolyte balance, nutrient requirements, disease state, and possible routes available for administration. Enteral formulas may be categorized into the monomeric (which contain free amino acids with or without peptides, with modified fat) and the polymeric formulas. Most enteral formulas fall in the semi-synthetic polymeric formulas, which are more cost effective but require patients to have digestive capability. Monomeric formulas are for patients with malabsorption, such as short-gut syndrome. Because of the cost associated with monomeric formulas, polymeric formulas should be tried first. For instance, in patients with pancreatitis, instead of using monomeric formulas, adding pancreatic enzyme tablets may help with polymeric tube feed tolerance. If the patient
TABLE 65.3
AN EXAMPLE OF MANAGEMENT GUIDELINES FOR METABOLIC COMPLICATIONS IN ADULTS INDUCED BY PARENTERAL NUTRITION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>&gt;200 mg/dL Once daily requirements of insulin are known from the insulin sliding scale, add 50%–75% into TPN. Consider insulin drip if blood sugar is uncontrolled, or if patient is edematous with unreliable absorption of subcutaneous insulin. Goal blood sugar is 80–110 mg/dL in critically ill surgical patients.</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>&lt;80 mg/dL If related to sudden discontinuance of TPN, administer D10W or D10NS at the same rate as the TPN. If related to insulin in TPN, initiate continuous glucose supplement (e.g., D10W). If glucose is still below desirable level, discontinue TPN and hang D10W or D10NS at the same rate as the TPN.</td>
</tr>
<tr>
<td><strong>Hypernatremia</strong></td>
<td>&gt;150 mEq/L If hypovolemic, give isotonic or hypotonic fluid depending on degree of hypovolemia. If euvoletic or hypervolemic, reduce sodium from TPN and/or other sources.</td>
</tr>
<tr>
<td><strong>Hyponatremia</strong></td>
<td>&lt;130 mEq/L If hypervolemic, restrict fluid intake ± diuretics; if euvoletic/hypovolemic, increase sodium content in TPN; if hypovolemic, give additional isotonic fluid.</td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
<td>&gt;5 mEq/L If TPN related and patient symptomatic, discontinue TPN and initiate D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease K+ in TPN and other sources.</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>&lt;3.5 mEq/L Give KCl bolus either IV or enterally (4 mEq for each 0.1 g of K+; maximum IV KCl concentration is 20 mEq/50 mL via central venous access and 10 mEq/50 mL via peripheral vein). Add K+ in TPN.</td>
</tr>
<tr>
<td><strong>Hypomagnesemia</strong></td>
<td>&gt;2.6 mEq/L If TPN related and patient is symptomatic, discontinue TPN and start D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease Mg2+ in TPN.</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td>&lt;1.8 mEq/L If TPN related and patient is asymptomatic, discontinue TPN and initiate D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease Ca2+ in TPN. Check ionized calcium in critically ill patients.</td>
</tr>
<tr>
<td><strong>Hypocalcemia</strong></td>
<td>&gt;10.2 mg/dL If TPN related and patient is symptomatic, discontinue TPN and initiate D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, decrease Ca2+ in TPN.</td>
</tr>
<tr>
<td><strong>Hypokalcemia</strong></td>
<td>&lt;8.5 mg/dL Correct for hyperalbuminemia [True Ca2+ = Ca2+ observed + 0.8 (4 – albumin observed)]. Increase Ca2+ in TPN if corrected Ca2+ is trending low. If hemodynamically unstable and/or critically ill, obtain an ionized calcium level (normal range 1.05–1.35 mg/dL). Give calcium chloride bolus via slow IV push if ionized calcium is low (&lt;1.05) and patient is symptomatic (e.g., hypotension). 1 g CaCl2 = 13.6 mEq; 1 g calcium gluconate = 4.7 mEq.</td>
</tr>
<tr>
<td><strong>Hyperphosphatemia</strong></td>
<td>&gt;4.8 mg/dL If TPN related and patient is symptomatic, discontinue TPN and run D10W or D10NS at the same rate as the TPN. If patient is asymptomatic, discontinue phosphate (PO₄³⁻) in TPN.</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td>&lt;2.4 mg/dL Phosphorus replacement should be given over 6 h to avoid hypotension. If level is &lt;1, give 30 mmol PO₄³⁻ × 2 doses IV plus check phosphorus level 1 h after end of infusion; if level is ≥1 but &lt;1.8, give 30 mmol PO₄³⁻ × 1 dose or enteral equivalent and check phosphorus level 1 h after end of infusion; if level is ≥1.8 but &lt;2.4, give 15 mmol PO₄³⁻ or enteral equivalent. One packet of Neutra-Phos enterally = 8 mmol of PO₄³⁻. Increase phosphorus in TPN.</td>
</tr>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td>pH &lt;7.4 HCO₃⁻ &lt;23 Consider increasing acetate-to-chloride ratio.</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td>pH &gt;7.4 HCO₃⁻ &gt;29 Consider increasing chloride-to-acetate ratio.</td>
</tr>
</tbody>
</table>

TPN, total parenteral nutrition; D10W, dextrose 10%; D10NS, dextrose 10% with 0.9% sodium chloride.

Each enteral feed formula has known amounts of kcal/mL, as well as g/L of protein. Once caloric and protein needs are assessed, the volume needed can be calculated. Unlike PN, in which the amounts of protein, dextrose, and fat can be easily modified, enteral feeding formulas are fixed. However, there are protein powders available if supplemental protein is necessary. Before starting any enteral feeds, feeding tube placement must be confirmed by abdominal radiography and documented continues to have absorption issues, then monomeric formulas could be substituted. Enteral formulas also vary by caloric density. In patients with chronic renal failure who require fluid restrictions, choosing polymeric formulas with high caloric density (high caloric-to-fluid ratio) may be helpful. Enteral formulas also differ in the amount of protein, the carbohydrate-to-fat ratio, and the fiber content.
in the orders. Once the enteral feeding formula has been selected, indicate initial strength (e.g., full or half-strength), initial rate in mL/hour, and desired progression regimen, followed by the goal rate. The rate can be started at 10 to 20 mL/hour and be advanced by 10- to 20-mL/hour every 8 hours as tolerated until goal (as long as residual is <200 mL via nasogastric tube or <100 mL via gastrostomy tube in 4 hours) (19). Many institutions have converted to a “closed system” to reduce the risk of microbial contaminations by minimizing the number of times the formula is manipulated. Enteral feedings start at full strength since a “closed system” will make it difficult to order partial-strength formulas.

When the patient is ready to transition over to a regular diet, similar strategies employed with the cyclic PN can be used. The patient may be converted to bolus feeding of the full-strength enteral formula with increases of 60 to 120 mL every 8 to 12 hours as tolerated up to goal volume. This simulates meals plus snacks (4). Bolus feedings are more physiologic, allowing the brain to stimulate sensations of hunger and satiety. When the patient is able to consume 60% of nutritional needs by mouth, the tube feeding can be discontinued (4).

**TABLE 65.4**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺, K⁺, Cl⁻, HCO₃⁻, BUN,</td>
<td>Daily</td>
</tr>
<tr>
<td>serum creatinine</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺, Mg²⁺, phosphorus, liver function tests</td>
<td>Two to three times per week</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>Weekly</td>
</tr>
<tr>
<td>CBC with differential</td>
<td>Weekly</td>
</tr>
<tr>
<td>Input/output</td>
<td>Daily</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>Weekly</td>
</tr>
<tr>
<td>Indirect calorimetry</td>
<td>As needed. Highly recommended in the following patients: Difficult to estimate accurately caloric requirements, inadequate response to nutrition support, and clinical signs of over- or underfeeding</td>
</tr>
<tr>
<td>24-h urine urea nitrogen</td>
<td>As needed. Highly recommended in the following patients: Difficult to estimate accurately protein requirements, inadequate response to nutrition support, and clinical signs of over- or underfeeding</td>
</tr>
<tr>
<td>Weight</td>
<td>Daily</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>As needed to keep blood sugar control of 80–110 mg/dL</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; CBC, complete blood count.


“DESIGNER” ENTERAL FEEDINGS: FACTS AND MYTHS

Designer enteral feedings or specialized formulas contain modified protein and other ingredients to assist patients in stressed states. Sometimes the ratio of carbohydrate to fat, and the sources of fat, may also be altered to achieve desired effects.

**Hepatic Formula**

Specialized hepatic formulas (e.g., NutriHep) differ from the standard formulas in two ways: the actual protein content is usually lower (around 40–46 g/L) and the ratio of branched-chain amino acids (BCAAs) to aromatic and ammonia-forming amino acids (AAAs) is higher in the hepatic formula. The theory is that in patients with liver dysfunction, depletion of BCAAs might enhance the passage of AAAs across the blood–brain barrier, resulting in the synthesis of false neurotransmitters (20). By giving a higher BCAA formula, the altered ratio is returned to a more normal state.

Although there are conflicting data, there is evidence of the beneficial effects of “special hepatic formulas” to support their use in the treatment of malnourished patients with advanced cirrhosis. A relatively recent multicenter, randomized, nutrient-controlled trial from 2003 demonstrated improved survival, serum albumin concentration, and quality of life in patients with cirrhosis when given BCAAs (21). A meta-analysis from 2003 reviewed 11 randomized trials and concluded that BCAAs improved hepatic encephalopathy in patients with chronic encephalopathy (22). There is evidence that in patients with acute overt encephalopathy, restriction or withdrawal of proteins may be necessary. Once encephalopathy has been reversed, adequate protein may be administered to target a positive nitrogen balance. Based on the available studies, and cost consideration of up to 20 times more, the “hepatic formula” should be restricted to patients who present with grade II or higher encephalopathy, or whose grade of encephalopathy worsens with the advancement standard enteral formulation.

**Renal Formula**

Enteral formulas in this class (e.g., Nepro) tend to be more caloric dense and low in electrolytes and mineral contents (especially potassium and phosphorous). The purpose of these modifications is to provide adequate nutrients but at the same time minimize complications such as uremia, fluid overload, and electrolyte accumulation. The older renal formulas differ from standard amino acids in that they were designed for patients...
who could not tolerate dialysis or for whom dialysis was being avoided; thus, the formulas tend to be enriched with essential amino acids (EAAs). The rationale with this admixture is that the urea from EAAs would be recycled to produce nonessential amino acids.

Evidence supporting the use of the older renal formulas is scant and of poor quality. In addition, the cost of the older renal formulas is 10 to 15 times that of standard polymeric formulas. These formulas have now been replaced with standard polymeric formulas since most patients with acute renal failure are now being dialyzed or are receiving CRRT. The new renal formulas continue to be more calorie dense (usually 2 kcal/mL) with minimal electrolytes or additives (K⁺, Mg⁺, PO₄⁻) that could accumulate in renal failure. They are appropriate for patients whose serum electrolyte and mineral levels are difficult to control.

**Pulmonary Formula**

Respiratory quotient (RQ) is defined as the mole of carbon dioxide produced per mole of oxygen consumed (VCO₂/VO₂). Pulmonary formulas (e.g., PulmoCare) are designed to decrease carbon dioxide by providing the fuel substrate with the lower respiratory quotient (see Table 63.2). To achieve this, the manufacturer decreases the carbohydrate-to-fat ratio to achieve fat calories of about 38% to 55%. By decreasing the carbohydrates (RQ = 1)–to–fat (RQ = 0.7) ratio, the assumption is that the carbon dioxide production is reduced as well.

Studies looking at the benefit of high-fat enteral feeds have been criticized as having a small sample size. One trial looking at high-fat enteral formula in 12 patients with chronic airflow obstruction suggests that the higher-fat formulas may be less likely to impair work performance in patients with chronic airflow obstruction (23). Another trial looking at 20 artificially ventilated patients demonstrated that the high-fat group spent 62 hours less time on the ventilator and the result was clinically significant (24). More recent evidence suggests that reducing total calories is more important than the source of calories, in terms of reducing carbon dioxide production (since the RQ of lipogenesis or overfeeding is 1–1.2) (25).

The source of fat has also changed over the years. Many formulas marketed today list canola oil and medium-chain triglyceride (MCT) oil as the primary sources of fat, compared to fat formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials. Whether formulas containing higher omega-6 fatty acids (precursor of arachidonic acid) that were used in the clinical trials.

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**Metabolic Stress (Critical Care) Formula**

The critical care formulas (e.g., Perative) are somewhat similar to the hepatic formulas in that both have a high percentage of BCAAs, which are the preferred substrate of muscles during critical illness. Differences include higher protein content and fewer aromatic amino acids in the critical care formulas compared to the hepatic formulas. The clinical trials looking at these formulas are small, and have been equivocal from the standpoint of nutritional markers. Overall, BCAA-enriched enteral formulas are not the current standard of practice. Because this class of enteral formula, like the immunomodulating formulas, may contain immune-enhancing agents (i.e., arginine), they must be used cautiously in critically ill septic patients (see next section on immuneonutrition timing).

**Immunomodulating Formula**

This class of enteral feedings is a subset of the metabolic stress formulas. Compared to the hepatic, renal, or pulmonary formulas, the formula designed to reduce inflammatory response (e.g., acute respiratory distress syndrome [ARDS]) is a more recent development. These so-called immunomodulating formulas are standard enteral formulas fortified with omega-3 fatty acids, nucleotides, arginine, and/or glutamine. The enteral feeding Oxepa contains no glutamine and arginine, but does contain 55% of calories as fat, of which the omega-6-to-omega-3 ratio is optimized to 2:1. Formula Impact has 23% of calories as fat, has arginine and glutamine, and contains 17.1% BCAAs in protein, and the omega-3-to-omega-6 ratio is 1.4:1. Formula Immun-Aid has 36% protein as BCAAs, contains arginine and glutamine, has 20% fat calories, and has an omega-6-to-omega-3 ratio of 2:1. (ratio similar to Oxepa). The theory behind this class of enteral feeds is that by minimizing omega-6 fatty acids and optimizing the ratio of omega-6 to omega-3 fatty acids, the inflammatory response is reduced, resulting in less lung injury.

Based on the early clinical trials and meta-analyses, which have mainly looked at Immun-Aid and Impact, it appears that surgical patients benefited most from this class of enteral formula. There was no effect on mortality in the meta-analyses, but there were significant reductions in infection rate, ventilator days, and hospital length of stay (26). More recent trials in this class of enteral feeds have focused on formula (i.e., Oxepa) enriched with eicosapentaenoic acid (EPA) from sardine oil and γ-linolenic acid (GLA) from borage oil plus antioxidants (vitamin E, vitamin C, β-carotene, taurine). One prospective, double-blind, placebo-controlled, randomized trial in 165 critically ill patients with severe sepsis found that this formula decreased mortality (19.4% absolute risk reduction), as well as decreased the number of days on the ventilator (27). Another prospective, randomized, controlled trial looking at enteral diet enriched with EPA + GLA in 100 patients with acute lung injury concluded that the formula reduced the length of time on the ventilator (28). Despite the many pieces of evidence pointing toward the benefit of immunomodulating formulas, it does have to be used with caution and at the right time. This will be discussed later in the chapter.

**Glycemic Control Formula**

The glycemic control enteral formulas are very similar to the pulmonary formulas in their design. The carbohydrate (35%–40%)-to-fat (40%–50%) ratio is reduced compared to standard formulas, with varying ratios of omega-6 to omega-3 fatty acids (e.g., Glucerna). This modification results in a greater proportion of fat calories than recommended (American Dietetic Association recommends ≤30% of calories from fat [29]). Various soluble fibers and/or soy polysaccharides are also added to the glycemic enteral formulas.
Clinical trials looking into the use of these specialty formulas in critically ill patients are limited. As with the polynucleotides, the high fat content in the glycemic formulas can decrease stomach emptying, which could decrease tolerance to these formulas even more in patients with diabetic gastroparesis. If glycemic control is needed, consider insulin drip. More studies are needed before these formulas can be recommended.

**TIMING OF SPECIALIZED ENTERAL FEEDING (IMMUNONUTRITION) AND MANIPULATION OF IMMUNE AND INFLAMMATORY SYSTEM**

Immunonutrition enteral feedings (e.g., Impact and Immun-Aid) are formulas containing nutrients that have been shown to influence immunologic and inflammatory responses in humans. These so-called immune-enhancing agents usually include the following: glutamine, arginine, omega-3 fatty acids, nucleotides, and antioxidants. Heyland et al. did an extensive meta-analysis to determine whether immunonutrition was safe and effective in critically ill patients. Although they were not able to find any mortality benefit, immunonutrition was associated with a statistically significant decrease in infectious complications and shorter length of hospital stay. When subgroup analyses of critically ill patients versus elective surgical patients were done, the results were surprising. There was a trend toward higher mortality in the critically ill patients, leading to the recommendation that immunonutrition not be used in critically ill patients until more clinical trials are conducted.

Bertolin et al. conducted a randomized multicenter trial comparing parenteral and early enteral nutrition containing immune-enhancing formula (Peripheral) in patients with and without severe sepsis (31,32). Results of an interim analysis indicated that mortality in severely septic patients receiving immune-enhancing enteral formulas was significantly higher than in those receiving parenteral nutrition (44.4% vs. 14.3%), and the study was aborted. Interestingly, in patients without sepsis, there was no 28-day mortality difference between the patients receiving parenteral nutrition versus immune-enhancing enteral formulas. However, those receiving immunonutrition had fewer episodes of septic shock, and the ICU length of stay was 4 days shorter.

Based on these studies, immunonutrition formulas should be used with caution in critically ill septic patients. Based on expert opinions, the immune-modulating nutrient likely to be responsible for the excess harm is arginine (see later), which has not been well studied in a randomized, clinical fashion in critically ill patients. In critically ill nonseptic patients, immune-enhancing formulas appear to be beneficial if started within 48 hours.

**IMMUNOMODULATORS**

**Glutamine**

Normally nonessential, glutamine becomes conditionally essential during times of high stress as evidenced by a decrease in glutamine concentration in the body during this period (34). Glutamine comes in the free form (unstable in solution, so only found in dried form) and protein-bound form as seen in all protein sources used in enteral formulas. Glutamine is an important amino acid because of its involvement in many vital functions, such as (a) gluconeogenesis; (b) synthesis of glycogen, nucleotides, nucleic acid, and urea; (c) ammoniagenesis; and (d) ammonia reduction (34). Glutamine is also the preferred fuel substrate for rapidly dividing cells in both the small intestine mucosa and the immune system (34). Furthermore, glutamine plays a big part in the antioxidation process, since it is the precursor of glutathione, a strong antioxidant (35).

In critically ill patients, about 30 g/day or 0.5 g/kg/day of glutamine is needed to meet both basal and increased enterocyte requirements (35).

A meta-analysis looking at 14 randomized trials concluded that glutamine supplementation in critically ill patients may be associated with a reduction in complication and mortality rates (35). In the same meta-analysis, glutamine supplementation in surgical patients may be associated with a reduction in infectious complication rates and shorter hospital stay without any adverse effect on mortality. Evidence from this meta-analysis also suggests that parenteral glutamine is more effective than enteral glutamine.

The effectiveness and benefits of glutamine supplementation are still not conclusive. A recent prospective but unblended study examining the benefit of enteral glutamine supplementation in 185 surgical ICU patients failed to detect a mortality difference between the control and treatment group (36).

**Arginine**

Like glutamine, many would consider arginine also to be a conditionally essential amino acid. About 5% to 6% of arginine comes from intake of proteins, and the rest is synthesized by the body via the urea cycle. Arginine is important in ammonia detoxification, as well as producing nitric oxide, which, among other things, mediates vasodilatory effects of endotoxin (37). Arginine supplementation has been purported to enhance wound healing in humans, mainly via improvements in extravascular markers of immune function (e.g., CD4 count) rather than outcome measures like infection rates (38).

Most human studies have largely been conducted using immune-enhancing diets containing relatively high amounts of L-arginine. The optimal dose of arginine in the critically ill patient is unknown, but a dose of up to 30 g/day is generally well tolerated by relatively healthy people (39).

Although evidence is not robust, arginine supplementation is capable of promoting an increase in nitric oxide production, which can lead to vascular smooth muscle dilation (36). Given this theoretical potential for harm, the clinician should use arginine-containing formulas with caution in critically ill septic patients (31,33,40).

**Nucleotides**

Nucleotides are structural units for nucleic acids and various enzymes involved in energy transfer. They are essential for the formation of new cells (e.g., intestinal epithelium) and...
in the synthesis of protein, lipids, and carbohydrates. Nucleotides are of interest because supplementation of infant formulas with nucleotides was noted to enhance bifidobacteria growth in the gastrointestinal tract. Bifidobacteria decrease the colonic lumen pH and inhibit growth of enteric bacteria (41).

Studies involving nucleotide use in humans are very limited, and like arginine, the studies available often involve immune-enhancing diets fortified with nucleotides, making it difficult to determine the effects of the nucleotides per se. One prospective, controlled trial studied the effects of nucleotide-supplemented formula in 26 severely malnourished children (younger than 4 years old). Insulin-like growth factor (IGF-1), growth factor binding protein-3 (IGFBP-3), leptin, soluble leptin receptor (sOB-R), and other hormonal biomarkers were measured. Enteral formulas enriched with nucleotides were shown to have a notable effect on IGF-1 and IGFBP-3, which could stimulate the catch-up growth of severe malnourished infants and toddlers (42).

### Structured Lipids

Triglycerides are three fatty acid chains attached to a glycerol backbone. Structured lipids are triglycerides with combinations of long-, medium-, and short-chain fatty acids on a single glycerol backbone not found in nature. The intent of this chemical manipulation is to make a product that has improved absorption (compared to long-chain triglycerides), minimizes immune dysfunction, and can provide essential fatty acids (43). Structured lipids are not yet commercially available in intravenous forms, although it has been a component of immunomodulating enteral formulas.

### Antioxidant Therapy

Antioxidants such as vitamin C, vitamin E, selenium, and β-carotene are often found in immunomodulating formulas. The role of antioxidant supplementation during critical illness is unclear. Studies have shown that critically ill patients often have low serum concentrations of some antioxidants, the significance of which is still not clear (44,45). However, there is good evidence now to suggest that reactive oxygen species (ROS) induce direct oxidative tissue injury by means of peroxidation of cellular membranes, oxidation of critical enzymatic and structural proteins, and induction of apoptosis (44,45). Thus, the importance of antioxidants seems obvious. Nathens et al. conducted a prospective, observational clinical trial looking at 95 critically ill surgical patients (91% trauma patients) who were critically ill surgical patients (91% trauma patients) who were administered with vitamin E. 1,000 international units every 8 hours via nasogastric tube and vitamin C 1 g intravenously every 8 hours (46). This study found that early administration of vitamin E and vitamin C reduced the incidence of organ failure (47).

References


Poisonings are recognized in the earliest recorded history. The word *toxicology* is derived from the Greek terms *toxikos* (“bow”) and *toxikon* (“poison into which arrowsheads are dipped”) (1, 2). In the 16th century, scientist Paracelsus made the astute observation that still holds strong: “What is there that is not poison? All things are poison and nothing [is] without poison. Solely, the dose determines that a thing is not a poison” (3). Today, we share Paracelsus’ appreciation of the dose-response relationship. One need not look farther than ba-sic elements such as oxygen or water to see that all substances can act as a poison at a specified dose. In modern medicine, the unique challenges posed by poisoned patients were recognized with the opening of the first poison control center in Chicago in 1953 (4); today, all 50 states are served by poison control centers. Medical toxicology, the care of poisoned patients, was recognized as a subspecialty by the American Board of Medical Subspecialties in 1992.

The American Association of Poison Control Centers (AAPCC) maintains the National Poisoning and Exposure Database (NPED), consisting of data from every case reported to poison centers in the United States. This database suffers from obvious limitations. Many exposures go unre-ported. One investigator found that only 12% of poisoning deaths identified by the medical examiner were reported to poison centers (5). Those that are reported are usually unconfir-med. Nevertheless, the database is a useful source of epidemi-ologic information, giving us an estimation of the incidence of various exposures. The NPED categorizes exposures based on outcome, designating effects as minor, moderate, or major. Ma-jor effects are those where the patient exhibits signs or symp-toms as a result of exposure that is life threatening or results in significant disability or disfigurement; this category constitutes a large portion of intensive care unit (ICU) toxicology cases. In 2003, the AAPCC received nearly 2.5 million reports of ex-posures, including 16,545 major effects and 2,613 deaths (6). Thus, while fatalities are 0.005% of total exposures, a rough estimate of the incidence of poisoning in the United States re-pre-sents 7% of the sum of major exposures and fatalities.

Throughout this chapter, any substance introduced to the body will be referred to as a xenobiotic. The terms *drug* and *pharmaceutical* identify the subgroup of xenobiotics that are commercially produced, while a toxin is a xenobiotic produced by a biologic system, such as plant, animal, or fungi. An ex-pose occurs whenever a human comes into contact with a xenobiotic. Exposures may be dermal, oral, ophthalmic, or in-halational. *Poisoning,* *intoxication,* and toxicity characterize the harmful consequences of a xenobiotic exposure. Consis-tent use of these definitions should enhance the clarity of our discussion.
By the time the patient has reached a critical care unit, initial stabilization should already have occurred. Nevertheless, the initial approach to the poisoned patient deserves mention because the clinician should respond to any deterioration in the patient’s condition by going back to the basic principles of diagnostic and therapeutic approaches. A key principle in managing poisoned patients is summarized by the phrase “treat the patient, not the poison.” The management of the poisoned patients begins with addressing airway compromise, breathing, and circulatory problems. Vital signs should be obtained, and cardiac and respiratory monitoring should be applied and given supplemental oxygen. Significant vital signs abnormalities or oxygen desaturation should be addressed immediately. Bedside serum glucose concentration should be rapidly obtained in any patient with altered sensorium or an abnormal neurologic examination. In fact, hypoglycemia may present with almost any altered mental status including agitation, delirium, coma, seizure, or focal neurologic deficit. This condition, while common and easy to correct, can be life threatening if diagnosis is delayed or missed (see section on antidiabetic agents).

A thorough physical examination will identify the presence of a toxic syndrome, or “toxidrome.” The classic toxic syndromes (Table 66.1) can be differentiated based on vital signs, mental status, pupil size, and presence (or absence) of peristalsis, diaphoresis, and urinary retention. The physician should keep in mind that these toxic syndromes are archetypes. Because of coexisting assumption of other poisons or coexisting disease processes, patients do not always demonstrate the typical symptoms of a particular syndrome. For example, the practice of “speedballing” (concurrent heroin and cocaine abuse) might result in small, normal, or large pupils. Though identification of a toxic syndrome will not specifically identify the exact poison responsible, it will somewhat guide therapy. For instance, the presence of a sedative-hypnotic toxic syndrome (overdose) warrants support of the airway, whether the condition is a result of ethanol or diazepam abuse.

Electrocardiogram (ECG) should be obtained in most cases of suspected poisoning. In fact, several well-defined exposures (such as tricyclic antidepressants) will be identified based on a characteristic ECG. Xenobiotics such as cocaine or lidocaine can produce life-threatening dysrhythmias via direct myocardial effect. Xenobiotics can also produce dysrhythmias by causing an electrolyte abnormality. Exposure to hydrofluoric acid, even dermally, can result in hypocalcemia, resulting in QTc prolongation and torsades de pointes.

While most poisoned patients can be managed appropriately by physical examination and judicious use of laboratory studies alone, history should attempt to identify the specific xenobiotic exposure, the amount, the time and reason for exposure, and general medical history. At times, a specific antidote may be warranted based on the history (see Appendix).

A thoughtful use of laboratory studies is important in the management of poisoned patients. Electrolyte abnormalities complicate many severe poisonings. Therefore, serum chemistries are warranted for all critically ill patients. Blood gases andaminotransferases should be judiciously used as well. In contrast with the fundamental information provided in blood samples, a routine urine toxicologic screen rarely aids in management and is therefore not recommended. A urine toxicologic screen generally focuses on select drugs of abuse and omits the vast majority of potential toxins. Moreover, the assays included in the commonly used qualitative urine screen omits the vast majority of potential toxins. Moreover, the assays included in the commonly used qualitative urine screen have either too many false positives or false negatives. For example, fentanyl, a synthetic opioid, will not produce a positive result on an opiate screen, while dextromethorphan may yield a positive result for phencyclidine. Even a true positive result on a toxicologic screen is not necessarily informative. The cocaine assay, while remarkably specific, will remain positive for days after the clinical effects have subsided.

**Table 66.1**

<table>
<thead>
<tr>
<th>TOXIDROMES</th>
<th>BP</th>
<th>P</th>
<th>R</th>
<th>T</th>
<th>Mental status</th>
<th>Pupil size</th>
<th>Peristalsis</th>
<th>Diaphoresis</th>
<th>Primary treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>-/+</td>
<td>+/+</td>
<td>-/+</td>
<td>Delerium</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Benzo diazepines</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>+/+/+</td>
<td>+/+</td>
<td>-/-</td>
<td>Normal/depressed</td>
<td>+/+</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Atropine, oximes</td>
</tr>
<tr>
<td>Ethanol, sedative- hypnotic</td>
<td>↓</td>
<td>↓</td>
<td>+/–</td>
<td>Depressed</td>
<td>+/–</td>
<td>↓</td>
<td>↑</td>
<td>–</td>
<td>Airway support</td>
</tr>
<tr>
<td>Opioid</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Depressed</td>
<td>↓</td>
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<td>–</td>
<td>–</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Withdrawal from opioid</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Agitated</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Withdrawal from sedative-hypnotic</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Agitated, disoriented</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Withdrawal from opioids</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
<td>Normal, anxious</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Opioids</td>
</tr>
</tbody>
</table>

BP: blood pressure; P: pulse; R: respirations; T: temperature.

In contrast to "shotgun" urine toxicologic screening, the acetaminophen concentration should be obtained following all overdoses where self-harm was intended. In one series, 1 in 365 individuals with suicidal ingestion and a history negative for acetaminophen ingestion had a potentially hepatotoxic acetaminophen concentration (7).

**DETERMINING THE NEED FOR INTENSIVE CARE UNIT ADMISSION**

Criteria that are traditionally used to determine whether patients need critical care do not necessarily apply to poisoned patients. For most patients, disposition is determined by how "sick" the patient is. In contrast, patients poisoned by dangerous xenobiotics but who appear well may require precautionary ICU admission and monitoring.

The factors that influence the need for critical care can be divided into three general categories: (a) patient characteristics, (b) xenobiotic characteristics, and (c) hospital unit capabilities (8).

All unstable poisoned patients require ICU care. Patients with significant laboratory abnormalities, unresponsiveness, inability to protect the airway, dysrhythmias, or conduction abnormalities should be admitted to the ICU. Pre-existing medical conditions such as severe liver or renal insufficiency, congestive heart failure, or pregnancy may also influence disposition.

The disposition for minimally symptomatic patients is often determined by the xenobiotic involved rather than the clinical status of the patient. The most important considerations are the potential for deterioration or the requirement for a therapeutic agent with potentially adverse effects. Sustained-release products, potentially lethal doses, or xenobiotics that may cause dysrhythmias have the potential to cause rapid clinical deterioration. For this reason, asymptomatic patients with exposure to calcium channel blockers or sulfonylureas are often admitted to an ICU for observation. Similarly, when xenobiotics require a therapy that has the potential for adverse effects, such as high-dose atropine for organic phosphorus insecticides, ICU admission is appropriate.

Finally, the capabilities of the hospital as a whole influence the disposition of the patient. Time-consuming nursing activities, such as hourly bedside glucose checks or the administration of drug infusions, that may not be possible on general inpatient units are indications for ICU admission. When the admitting team or nursing staff is not familiar with the complications associated with a particular xenobiotic exposure, ICU admission may also be indicated.

**NONOPIOID ANALGESICS: ACETAMINOPHEN, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, AND SALICYLATES**

In 2005, the American Association of Poison Centers NPED received 227,496 reports of exposures to analgesics (6). The extensive availability of these drugs contributes to their prevalence in both suicidal ingestions and unintentional pediatric ingestions. Although they are generally safe when used correctly, the widely held misconception that these pharmacueticals are harmless undoubtedly contribute to their potential for causing harm.

Over 100,000 reports of acetaminophen exposure were received by the NPED in 2005 (6). The vast majority of exposures do not result in significant morbidity, and only 333 were fatal and another 3,310 considered major. Although the data set is controversial, acetaminophen is estimated to be responsible for 31% of all cases of acute liver failure in the United States (9). Acetaminophen ingestions require ICU admission when hepatotoxicity is established.

Acetaminophen is an analgesic and antipyretic with less anti-inflammatory activity than the nonsteroidal anti-inflammatory drugs. The analgesic effects of acetaminophen are mediated by central cyclo-oxygenase (COX-2) and prostaglandin synthase (10) inhibition. Less than 5% of acetaminophen is eliminated unchanged in the urine. The metabolism of acetaminophen occurs principally in the liver. Ninety percent of absorbed acetaminophen undergoes hepatic conjugation with either glucuronide or sulfate to produce inactive metabolites. The remainder (5%–15%) is oxidized by the cytochrome P450, forming N-acetyl-p-benzoquinonemine (NAPQI), a toxic oxidant (11). Thiol-containing compounds, such as reduced glutathione, are used as electron donors to detoxify NAPQI.

The single dose of acetaminophen generally thought to be required to produce toxicity is ≥150 mg/kg (11). In overdose, absorption of acetaminophen may be delayed, although peak absorption generally occurs at 2 hours, and rarely after 4 hours (12,13). Absorption may be expected to be further delayed in the presence of peristalsis-decreasing opioid or anticholinergic congestants, or if the acetaminophen is formulated for extended release. In overdose, metabolism by sulfation becomes saturated, and the formation of NAPQI exceeds that which can be detoxified by available glutathione (14). Because the toxic metabolite is formed in the liver, hepatic toxicity is the key clinical feature. N-acetyl-p-kysteine (NAC), the key to management of acetaminophen poisoning, acts as a precursor to glutathione synthesis, a substrate for sulfation; it directly binds to NAPQI itself, and enhances the reduction of NAPQI to acetaminophen (15).

**Clinical Manifestations**

Acute acetaminophen toxicity has been divided into four clinical stages (16). Not every untreated patient will advance through each of these stages. Spontaneous improvement is possible at any point, but the stages of toxicity serve as a useful guide to the progression of symptoms. During stage I, the patient is either asymptomatic or has nonspecific clinical findings (nausea, vomiting, malaise), and no laboratory abnormalities are recognized. Stage II begins with the onset of liver injury, generally within 24 hours but always within 36 hours of ingestion (17). Symptoms are similar to other causes of hepatitis.
Initial laboratory findings include elevated aminotransferases (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]), but progress to signs of hepatic dysfunction, including prolonged prothrombin time (PT), metabolic acidosis, and hypoglycemia. Stage III represents the time of peak hepatotoxicity, usually 72 to 96 hours from ingestion. While AST and ALT may ultimately exceed 10,000 IU/L, creatinine, lactate, phosphate, and PT are better indicators of prognosis. Fatalities usually occur within 3 to 5 days of ingestion. When death does not occur, hepatic recovery is referred to as stage IV. Hepatic regeneration will be histologically and functionally complete in survivors.

**Management**

N-acetylcysteine is the key to managing acetaminophen poisoning. Because of its proven efficacy, decontamination with activated charcoal should only be considered if significant coingestants are expected. NAC is available for both oral and intravenous administration. The oral protocol for acute ingestions is a 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours for a total of 72 hours. The intravenous regimen is 130 mg/kg over 45 minutes, followed by 30 mg/kg every 4 hours, and then 100 mg/kg over 16 hours. Both regimens have equal efficacy for simple acute ingestion, but the intravenous regimen has the advantage of a shorter course, and is the only route that has been studied adequately in patients with hepatic failure. Unlike oral NAC, parenteral NAC carries the risk of anaphylactoid reactions. The duration and route of treatment are determined by the type of presentation.

The simple, acute ingestion occurs when a single dose of acetaminophen is ingested over a short period of time, within 24 hours of presentation. There is little controversy in managing this type of ingestion. The serum acetaminophen concentration should be plotted against the number of hours following ingestion on the Rumack-Matthew nomogram to determine whether treatment with NAC is necessary (18). The treatment line is a sensitive, but not specific, predictor of hepatotoxicity. The currently recommended line intersects 150 µg/mL at 4 hours, incorporating a 25% safety margin over the original nomogram line, which was itself nearly 100% sensitive for predicting hepatotoxicity. When the concentration at a specific time is plotted above the line, treatment is required. When treatment is initiated within 8 hours of ingestion, NAC has complete efficacy in preventing hepatotoxicity (19). NAC should be started immediately in any patient with suspected acetaminophen poisoning when the laboratory result for the acetaminophen concentration is not expected to be available within 8 hours of the initial ingestion. Once the serum acetaminophen concentration is available, the decision whether to continue the NAC can be made based on the nomogram (Fig. 66.1). When there is uncertainty with regard to the exact time of ingestion, the physician should use the most conservative estimate (i.e., the earliest possible time) when using the nomogram. The risk of inadvertently failing to treat because of an incorrect history is mitigated by the safety margin associated with the nomogram.

The literature is less clear on the indications for the use of NAC for hepatotoxicity following suspected chronic acetaminophen use. The vast majority of people who take acetaminophen have no adverse clinical manifestations. Clinical trials involving daily dosing of 4 g of acetaminophen in both alcoholics and nonalcoholics showed that patients either have normal aminotransferase concentrations or very minor increases (20,21). Despite its safety, hepatotoxicity from chronic use occurs. Because chronic acetaminophen use often occurs in the setting of comorbid conditions, the diagnosis can be difficult to establish with certainty. NAC should be administered to all patients with suspected acetaminophen hepatotoxicity until the diagnosis has been excluded.

The nomogram cannot be used for patients who present more than 24 hours after ingestion. In such cases, NAC should be started immediately upon presentation. If the patient has both an undetectable acetaminophen concentration and normal aminotransferases, acetaminophen overdose is highly unlikely, and NAC need not be continued. If either acetaminophen or aminotransferase concentrations are elevated (even minimally so), the patient should be administered 20 hours of IV NAC. Following the treatment period, aminotransferase and acetaminophen concentrations are elevated (even minimally so), the patient should be administered 20 hours of IV NAC. Following the treatment period, aminotransferase and acetaminophen concentrations should be obtained again. At this point, if the aminotransferase concentrations are only minimally elevated, the patient was either minimally poisoned or acetaminophen was not the cause of the liver damage.

When acetaminophen–induced hepatotoxicity is encountered, intravenous NAC should be administered as described above, but the maintenance dose should be continued until clinical improvement, liver transplantation, or death occur. Even in the presence of fulminant hepatic failure, IV NAC has been shown to decrease mortality, cerebral edema, and the need for vasopressors (22).

**Hepatic Transplantation**

Generally, patients with significant acetaminophen poisoning will have AST and ALT concentrations >1,000 IU/L by 24 to 48 hours after ingestion. The decision to perform hepatic...
transplantation is particularly difficult in these patients, be-
cause those who survive without a transplant will make a com-
plete recovery, while the long-term complications of a trans-
plant are significant. Under ideal conditions, the clinician could
determine immediately which patients would survive without a transplant and which would not, so that the appropriate pa-
tients could be listed for a liver transplant and the procedure could be performed before irreversible clinical deterioration.
In practice, it is not always clear. Several prognostic criteria are available. The King’s College Hospital Criteria suggest that a phosphorus level of less than 0.7 mmol/L, a creatinine level of more than 3.3 mg/dL, and a grade III or IV encephalopathy are predictive of death in the absence of a transplant (23). Serum phosphorus has also been shown to be a good predictor. A 48-
hour serum phosphorus concentration greater than 1.2 mmol/L has been shown to be sensitive and specific for predicting the need for transplant and the probability of death from acetonaminophen hepatotoxicity (24). Presumably, a low or normal phosphorus concentration is evidence that the phosphorus is being utilized by hepatocytes for adenosine triphosphate (ATP) generation.

### SALICYLATES AND OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available both with and without prescription for relief of in-
flammation, pain, and fever. Salicylates are a subgroup of NSAIDs that have unique features of toxicity and require dis-
tinct management. In this chapter, we will use the term NSAID in reference to the nonsalicylate NSAIDs. ICU admission is required when patients present with metabolic acidosis and hemodynamic instability, or if they require bicarbonate infusion or frequent measurements of salicylate concentration.

The therapeutic effects of salicylates and NSAIDs result from the inhibition of cyclooxygenase (COX), a mediator of prostaglandin synthesis. The myriad medications in this class preclude discussion of the individual pharmacokinetic char-
acteristics. In general, they are renally eliminated. Because they are designed to promote fast relief, therapeutic doses of the immediate-release drugs produce significant concentrations within an hour. However, when taken in overdose or as enteric-coated or sustained-release formulations, absorption may be greatly delayed, and maximal serum concentrations may not be observed for hours after the ingestion.

In addition to these effects, salicylates also uncouple oxida-
tive phosphorylation, meaning that some of the proton gradient across the mitochondrial matrix is dissipated in the formation of heat, rather than ATP, forcing the production of lactate.

### Clinical Manifestations of Salicylate Poisoning

Acute salicylate poisoning may cause epigastric pain, nausea, and vomiting. Salicylates induce hyperventilation (both tachyp-
ea and hyperpnea) by direct stimulation of the brainstem respiratory center (25). Neurologic signs and symptoms of sal-
icylate poisoning range from mild to severe, and include tinni-
tus, delirium, coma, and seizure. The initial feature of toxicity is primary respiratory alkalosis. A primary metabolic acidosis is characterized by the presence of lactic acid, ketoads, and salicylic acids (26). The net result is an increased anion gap metabolic acidosis. The simultaneous presence of a respiratory alkalosis and metabolic acidosis can be difficult to interpret. Be-
cause the respiratory alkalosis initially predominates in adults, the presence of an acidemia or even normal pH indicates ad-
vanced poisoning.

### Management of Salicylate Poisoning

The key principles for management of salicylate poisoning are to minimize absorption, speed elimination, and minimize redis-
tribution to tissues. Gastric emptying should only be attempted if a significant amount of drug is expected to be present in the stomach. Activated charcoal, 1 g/kg, should be administered every 4 hours if it can be given safely. Salicylates cause py-
lorospasm and may form concretions in overdose, leading to delayed absorption. Multiple-dose activated charcoal (MDAC) not only prevents delayed absorption, but also may speed elim-
ination of salicylates by disrupting the enteroenteric circulation of the drug (27). Serum chemistry, venous or arterial blood gas, and salicylate concentration should be obtained every 2 hours until the salicylate concentration demonstrates an interval de-
crease.

Moderately poisoned patients (increased anion gap or a sal-
icylate concentration greater than 40 mg/dL) should also have blood and urine alkalinated with sodium bicarbonate. As a weak acid (pKa 3.5), salicylates will be ionized in an alka-
line environment and “trapped” (i.e., unable to passively move through lipid membranes). Ionization prevents salicylate in the proximal tubule from diffusing into the plasma and salicylate in the plasma from diffusing into tissues, such as the brain (28). Alkalization can be achieved with an infusion of sodium bi-
carbonate of 150 mL/kg in 1 L of DSW at twice the maintenance rate. The urine pH should be maintained from 7.5 to 8.0 and systemic arterial pH between 7.45 and 7.55. Close attention should be paid to potassium repletion, as low serum potassium will cause preferential reabsorption of potassium over hydro-
gen ions in the proximal tubule and compromise attempts to alkalinate the urine (29). Endotracheal intubation and seda-
tion should be avoided whenever possible. The tachypnea and
hyperlactate of salicylate poisoning does not necessarily repre-
sent “tiring,” and produces a helpful alkalosis. When intu-
bation is unavoidable, patients should be administered 1 to
2 mEq/kg of bicarbonate prior to the procedure, intubated
quickly, and hyperventilated afterward to avoid respiratory aci-
dosis.

Early consultation with a nephrologist is recommended for
seriously ill patients. Extracorporeal elimination is reserved
for patients who are very ill, those who cannot tolerate al-
kalization, or those with serum concentrations so elevated
that their clinical status is expected to deteriorate. We recom-
mend hemodialysis for severe acid-base disturbances, mental
status changes, inability to tolerate alkalization (renal failure
or congestive heart failure), and serum concentrations of 100
mg/dL after acute poisoning and 60 mg/dL in chronic poisoning (Table 66.2).

**Clinical Manifestations of Nonsteroidal
Anti-inflammatory Drug Poisoning**

NSAIDs are considered safer than salicylates in therapeutic
dosing. An acute overdose of NSAIDs can cause gastric in-
jury. While chronic NSAID use is associated with interstitial
nephritis, nephritic syndrome, or analgesic nephropathy, acute
overdose is sometimes accompanied by a reversible azotemia
caused by vasoconstriction from decreased prostaglandin pro-
duction (30). In severe overdose, the most consequential effects
are elevated anion gap metabolic acidosis, coma, and hypoten-
sion (31).

**Management of Nonsteroidal
Anti-inflammatory Drug Poisoning**

Activated charcoal should be administered if the patient
currently presents within several hours of overdose. Good support-
ive care is the mainstay of therapy after NSAID overdose.
NSAID elimination is not increased with alkalization, and
NSAIDs’ high degree of protein binding precludes removal with
hemodialysis. Hemodialysis has been used to correct acidemia
and electrolyte abnormalities in patients with multigorgan sys-
tem failure.

**PSYCHIATRIC MEDICATIONS**

Psychiatric medications represent a disproportionate number
of poisonings in the United States. Antidepressants, antipsy-
chotics, and sedative-hypnotics accounted for more than half
of all deaths reported to poison control centers in 2003 (6).
This high mortality figure is a function of the prevalence of
these ingestions, as these drugs do not have a high case-fatality
rate. With sound supportive care, most patients can be man-
aged successfully.

**Antipsychotic Medications**

The antipsychotics are categorized as either typical or atyp-
ical. The typical antipsychotics, which include haloperidol,
chlorpromazine, and thioridazine, antagonize dopamine pri-
marily at the D2 receptor. The newer medications, the atypical
drugs, are exemplified by clozapine, olanzapine, quetiapine,
risperidone, and ziprasidone, which have less dopaminergic
antagonism and more serotonergic effects than the typical an-
tipsychotics. When antipsychotic medications produce coma,
conduction abnormalities, or hyperthermia, these patients re-
quire ICU admission.

**Clinical Manifestations of Overdose**

The antipsychotics are a diverse group of medications, al-
though useful generalizations can be made about their clinical
manifestations. All produce sedation in overdose, though respir-
atory depression is usually not consequential. The drugs have
varying degrees of muscarinic and α-adrenergic antagonism,
often resulting in tachycardia and moderate hypotension (32).
Many of the typical antipsychotics have type IA antidyssyrth-
amic properties. Most of the typical and a few of the atypical
drugs (notably ziprasidone) can cause QTc prolongation and
torsades de pointes (33,34). Management of overdose of the
antipsychotics generally only requires supportive care.

**Clinical Manifestations of the Neuroleptic
Malignant Syndrome**

The dopamine antagonism required for control of psychosis
can cause a group of distinct movement disorders that range
in severity from mild to life threatening. These conditions—
dystonia, akathisia, parkinsonism, tardive dyskinesia, and neu-
roleptic malignant syndrome (NMS)—are more likely to occur
in the presence of the typical antipsychotics, although the atypical
antipsychotics can cause them as well. The first four con-
ditions mentioned above are of less concern to the intensivist
than NMS, and will not be discussed.

NMS is the most consequential of the movement disorders
associated with the antipsychotics. The syndrome is character-
ized by the presence of altered mental status, muscular rigidity,
hyperthermia, and autonomic dysfunction (35). While symp-
toms usually begin within weeks of starting treatment, they do
occur in individuals that are taking the drug on a chronic basis.
Risk factors include young age, male gender, extracellular fluid
volume contraction, use of high-potency antipsychotics, depot

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**TABLE 66.2**

<table>
<thead>
<tr>
<th>INDICATIONS FOR HEMODIALYSIS IN SALICYLATE POISONING</th>
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</thead>
<tbody>
<tr>
<td>Renal failure</td>
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<tr>
<td>Congestive heart failure (relative)</td>
</tr>
<tr>
<td>Acute lung injury</td>
</tr>
<tr>
<td>Persistent CNS disturbances</td>
</tr>
<tr>
<td>Progressive deterioration in vital signs</td>
</tr>
<tr>
<td>Severe acid-base or electrolyte imbalance, despite</td>
</tr>
<tr>
<td>appropriate treatment</td>
</tr>
<tr>
<td>Hepatic compromise with coagulopathy</td>
</tr>
<tr>
<td>Salicylate concentration (acute) &gt; 100 mg/dL or (chronic) &gt; 60 mg/dL</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
drug preparations, concomitant lithium use, rapid increase in dose, or simultaneous use of multiple drugs (34). Diagnosis is not always clear because there is no reference standard. The differential diagnosis of hyperthermia and altered mental status is very broad. Other diagnoses to consider include infection, environmental hyperthermia, hyperpyrexia, serotonin syndrome, ethanol and sedative-hypnotic withdrawal, sympathomimetic intoxication, and antiadrenergic intoxication.

Management of NMS begins with immediate treatment of life-threatening hyperthermia. Ice-water immersion and paralysis by neuromuscular blockade should not be delayed if temperature is > 106 °F (41.1 °C). In instances of environmental hyperthermia, a delay of cooling longer than 30 minutes has been associated with significant morbidity and mortality (36). Benzodiazepines should be titrated to sedation and muscle relaxation. When present, rhabdomyolysis, electrolyte disorders, and hypotenison should be aggressively treated.

Bromocriptine, a centrally acting dopamine agonist given at 2.5 to 10 mg three to four times a day, may be of theoretical benefit even though it is not well studied. NMS may not be controlled for days after the introduction of bromocriptine. After signs and symptoms begin to improve, bromocriptine should be decreased by no more than 10% a day since decreasing the dose too rapidly may precipitate a relapse of NMS.

There is no evidence for the antidotal use of dantrolene in the management of NMS. Dantrolene is the drug of choice in malignant hyperthermia, a disorder affecting the sarcoplasmic reticulum that occurs in susceptible individuals receiving inhalational anesthetics or succinylcholine that some confuse with neuroleptic malignant syndrome because of their similar mic reticulum that occurs in susceptible individuals receiving inhalational anesthetics or succinylcholine that some confuse with neuroleptic malignant syndrome because of their similar names and clinical manifestations.

Chapter 66: Toxicology

Benzodiazepines

In 2005, the AAPCC reported 3,018 major effects and 124 fatalities from benzodiazepines (6). Benzodiazepines are widely used for their sedative, anxiolytic, and anticonvulsant properties. All these effects result from increasing the frequency of opening of γ-aminobutyric acid (GABA)-mediated chloride channels in the central nervous system (CNS) (37). In overdose, these drugs produce somnolence, coma, and minimal decreases in blood pressure, heart rate, and respiratory rate.

Management of benzodiazepine overdose is supportive. Care of the comatose patient should focus on supporting the airway and blood pressure while waiting for the drug to be eliminated. There is a limited role for flumazenil, a competitive benzodiazepine antagonist; flumazenil can precipitate withdrawal in individuals who are tolerant to benzodiazepines and induce seizures in those with seizure disorders (38,39). Flumazenil may be indicated in patients without tolerance to benzodiazepines who suffer from a pure benzodiazepine overdose. Benzodiazepine overdoses in children may meet these criteria. When indicated, flumazenil should be given intravenously, 0.1 mg/min, up to 1 mg. The dose can be repeated if the clinical response is inadequate. Because the duration of the effect of flumazenil is shorter than the effect of the benzodiazepine, recurrence of symptoms should be expected. Alternatively, redosing or a continuous IV infusion at 0.1 to 1.0 mg/hour may be administered. The clinician should determine that the risk-benefit analysis of flumazenil favors administration of the drug.

If there is any doubt as to whether the patient has tolerance to benzodiazepines, flumazenil should not be administered. Benzodiazepine poisoning can be managed effectively and safely with supportive care only, but benzodiazepine withdrawal precipitated by flumazenil can be life threatening.

Cyclic Antidepressants

Until the introduction of the selective serotonin reuptake inhibitors (SSRIs), the cyclic antidepressants were the principal pharmacologic treatment available for depression. Roughly 12% of the 11,198 cyclic antidepressant exposures reported to the AAPCC in 2005 had either a major outcome or fatal- ity. While the cyclic antidepressants differ slightly from each other in their receptor affinities, they can be treated as a group.

The CAs are usually absorbed within hours of ingestion, although the antimuscarinic effects may delay absorption in overdose. The drugs also exhibit α-adrenergic antagonism, inhibition of reuptake of norepinephrine, and anticholinergic properties. Acting as type IA antidyssrhythmics, CAs block sodium entry into myocytes during phase 0 of depolarization.

Clinical Manifestations

Important CNS effects include lethargy, delirium, coma, and seizures. Tachycardia and hypotenison develop early in toxicity. The IA antidyssrhythmic properties cause prolongation of the QRS interval. CAs also produce a characteristic rightward shift of the axis in the terminal portion of the QRS, best seen as an R wave in the terminal 40 msec of lead aVR (40) (Fig. 66.2).

Management

Gastrointestinal decontamination should be considered in every patient. If the history suggests a recent large ingestion, gastric lavage may be attempted. Acute ingestions of 10 to 20 mg/kg of most CAs can cause significant poisoning (41). Activated charcoal should be administered. Serum drug concentrations may be obtained but do not correlate well with toxicity (42).

The ECG is the most important diagnostic test when managing CA overdose. A terminal 40-msec QRS axis of 130 to 180° is very broad. Other diagnoses to consider include infec-

FIGURE 66.2. Terminal elevation of aVR and QRS prolongation.

Lithium is used in the treatment of bipolar affective disorders. Patients will require ICU admission when they have signs of CNS toxicity, do not tolerate fluid therapy, or have serum concentrations ≥2 mmol/L, which may result in rapid deterioration. Of 3,559 exposures reported to the AAPCC, 5.7% were classified as major or fatal.

**Pharmacology**

Lithium is thought to increase serotonin release and increase receptor sensitivity to serotonin, as well as modulate the effects of norepinephrine on its second-messenger system (47). Like sodium, lithium is a monovalent cation. The kidney handles lithium and sodium similarly. Lithium is freely filtered by the glomerulus, and 80% is reabsorbed, with 60% occurring in the proximal tubule (48). Immediate-release lithium preparations produce peak serum concentrations within hours, but sustained-release lithium may not peak for 6 to 12 hours. The generally accepted therapeutic range of lithium is 0.6 to 1.2 mmol/L, although in both overdose and therapeutic dosing, clinical signs and symptoms may serve as a better guide than the serum concentration.

**Clinical Manifestations of Overdose**

Acute and chronic lithium toxicity have similar neurologic features, although acute toxicity is usually associated with significant gastrointestinal manifestations. Acute toxicity occurs when an individual without a body burden of lithium takes a supratherapeutic dose of the drug. Chronic toxicity is usually the result of decreased elimination of the drug in a patient who is receiving a fixed dose (e.g., after developing renal insufficiency). Acute-on-chronic toxicity occurs when a patient with a pre-existent total body drug takes a supratherapeutic dose. In acute toxicity, a large ingestion of lithium—a gastrointestinal irritant—will initially cause gastrointestinal symptoms, such as vomiting and diarrhea. Neurotoxicity (which is clinically more significant) will be delayed until the drug has been absorbed and is redistributed into the CNS. In chronic lithium toxicity, gastrointestinal symptoms may be completely absent. Neurotoxicity manifests itself as disorders of movement and alterations in mental status. In very mild toxicity, only a fine tremor will be present, but in more advanced poisoning, fasciculations, hyperreflexia, dysarthria, and nystagmus may be seen as well (48). Mental status changes range from confusion to coma and seizures (49).

Nephrogenic diabetes insipidus and hypothyroidism occur following chronic therapeutic lithium use but are not features of overdose. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a chronic neurologic disorder with many of the same features of lithium neurotoxicity. The distinction is that SILENT persists even when the body burden of lithium is eliminated. The mechanism is not completely elucidated but may involve demyelination. SILENT has been reported both as a result of chronic therapeutic use and as a sequel of lithium intoxication (50).

**Management**

Gastrointestinal decontamination should be considered after acute lithium toxicity. Since lithium does not bind to activated charcoal, activated charcoal should only be considered when a mixed overdose is suspected (51). When sustained-release preparations are ingested, whole bowel irrigation has been shown to decrease serum lithium concentration (52). Whole bowel irrigation can be performed by administering 2 liters of polyethylene glycol orally every hour (25 mL/kg/hour in children) until the rectal effluent is clear. After both acute and chronic toxicity, intravenous fluids should be given to optimize intravascular volume. The volume-depleted patient will have a decreased glomerular filtration rate and increased reabsorption
of lithium. When fluid deficits are restored, 0.9% saline can be administered at twice the maintenance rate or approximately 200 mL/hour in adults to aid in elimination of lithium.

Extracorporeal elimination may be necessary to treat lithium toxicity. Lithium can be removed by hemodialysis due to its low volume of distribution and limited protein binding. Although hemodialysis can only remove the lithium residing in the vascular compartment, the elimination of serum lithium will allow the remaining intracellular lithium to redistribute into the plasma. Thus, although lithium concentrations may rebound following dialysis, the tissue burden has actually decreased. The indications for dialysis are not universally agreed upon. Hemodialysis should be performed when there are signs of significant end-organ damage, when lithium cannot be eliminated without dialysis, or when the serum concentration is elevated such that severe toxicity is highly likely. We recommend dialysis when there is significant CNS toxicity such as coma, obtundation, coma, or seizures when a patient with milder toxicity cannot eliminate lithium efficiently (renal insufficiency) or tolerate saline resuscitation (congestive heart failure); or in the presence of a serum lithium concentration >4.0 mmol/L following acute poisoning or >2.5 mmol/L following chronic poisoning. Since repeat dialysis may be necessary, the clinician should reapply the above criteria 4 hours after dialysis is completed to determine if dialysis should be repeated.

A common clinical pitfall is to deny dialysis to patients with an elevated lithium concentration and signs of toxicity because consecutive lithium concentrations have shown a small decrease. The clinician concludes that the lithium will eventually be eliminated without dialysis, so dialysis should not be helpful. Furthermore, exposure to the toxic lithium levels may predispose the patient to SILENT. In other words, it is better to be exposed to a neurotoxin for a few hours than a few days. While this area is not adequately studied, it seems prudent to hemodialyze these patients.

**TOXICOLOGIC BRADYCARDIA: DIGOXIN, β-ADRENERGIC ANTAGONISTS, AND CALCIUM CHANNEL BLOCKERS**

In 2005, the AAPCC NPID reported more than 30,000 exposures to cardiovascular steroids (including digoxin), β-adrenergic antagonists, and calcium channel blockers. This figure includes 1,085 major outcomes and 167 fatalities (6). These xenobiotics have a narrow therapeutic index, drawing a fine line between therapeutic dosing and poisoning. The individuals who take these medications usually have underlying cardiovascular disease, making management of overdose even more challenging.

**Digoxin**

Digoxin is a cardioactive steroid derived from the foxglove plant. Though digoxin and digitoxin are the only pharmaceuticals in the class, plants such as celandine, yellow celandine, dogbane, and red squill contain cardioactive steroids with similar toxicity. While some of these plants cause a great deal of morbidity worldwide, this chapter will deal primarily with digoxin, which causes more morbidity than any other cardioactive steroid in North America. Of 2,828 reported exposures to cardiac steroid medications in 2005, 74% were classified as major or fatal (6). Digoxin has multiple therapeutic and toxic cardiovascular effects, all of which result from inhibition of the Na+-K+-ATPase. The Na+-K+-ATPase extrudes sodium from the myocardial cell, creating a sodium gradient that drives an Na+-Ca2+-mediated calcium influx through the sarcolemmal calcium channel (Fig. 66.3). Ca influx through this cell membrane triggers Ca release from the sarcoplasmic reticulum (SR); this is commonly called Ca-mediated release.

Digoxin also slows conduction through the sinoatrial (SA) and atrioventricular (AV) nodes, probably through direct and vagally mediated mechanisms (31). In therapeutic use, digoxin decreases heart rate and increases inotropy. In overdose, the increased intracellular Ca2+ brings the cell closer to threshold, resulting in increased automaticity.

Digoxin does not exert its therapeutic and toxic effects until it redistributes from the serum into the myocardium. Digoxin has a large volume of distribution, precluding elimination by hemodialysis. Digoxin is mostly eliminated renally, although there is some hepatic metabolism. The maximal effect from a therapeutic dose of digoxin is seen at 4 to 6 hours when administered orally and 1.5 to 3 hours when given intravenously.

**Clinical Manifestations**

Digoxin poisoning can be either acute or chronic. Acute toxicity occurs when an individual without a tissue burden of digoxin ingests a supratherapeutic dosage of the drug. Chronic toxicity usually occurs when an individual on a fixed dose of the drug loses the ability to excrete it effectively. Both syndromes have similar cardiovascular manifestations, but acute toxicity may feature more prominent gastrointestinal symptoms. Acute poisoning may result in nausea, vomiting, and abdominal pain, whereas chronic poisoning develops more insidiously. In addition to gastrointestinal symptoms, chronic poisoning may present with weakness, confusion, or delirium (54,55).

Bradycardia with a preserved blood pressure typically occurs in digoxin toxicity. The ECG is the most important test in establishing the diagnosis. Because digoxin has multiple cardiac effects, there is no single ECG manifestation that is consistently seen in patients with digoxin toxicity. Almost any rhythm is possible, with the exception of a rapidly conducted supraventricular rhythm. The most common rhythm disturbance on initial ECG is the presence of ventricular ectopy (56). The ECG could potentially exhibit increased automaticity from elevated resting potential, conduction disturbance from AV and SA nodal block, both, or neither. The ectopy may degrade into ventricular tachycardia or ventricular fibrillation. If conduction disturbance predominates, the ECG may demonstrate sinus bradycardia or varying degrees of AV block.

The laboratory provides clues to toxicity. The therapeutic range for digoxin is usually reported as 0.5 to 2.0 ng/mL. Serum digoxin concentration should be interpreted in the context of the history and ECG. Digoxin is a cardioactive steroid, and serum concentrations do not necessarily reflect the degree of poisoning. Digoxin requires several hours to redistribute from the serum to the tissues. Shortly after an acute ingestion, the serum concentration may overestimate toxicity, while a mild increase in...
serum concentration of a patient chronically on digoxin may underestimate the high extent of the increased tissue burden. Serum potassium concentration is a better predictor of illness following acute ingestions. A study of 91 digitoxin-poisoned patients performed in the pre-digoxin-specific antibody fragment era found no mortality when the potassium concentration was less than 5.0 mEq/L and 50% mortality when the potassium concentration was 5.0 to 5.5 mEq/L (57).

Management of Toxicity

Because acute toxicity can cause vomiting, activated charcoal and gastric lavage may be of limited value. Atropine can be given intravenously in 0.5-mg doses for bradycardia, although it is probably not important to "correct" the heart rate if the blood pressure is preserved. If necessary, potassium should be supplemented. Hypokalemia inhibits the function of the Na⁺-K⁺-ATPase, and thereby exacerbates digoxin poisoning. A pitfall in managing digoxin-poisoned patients is the administration of calcium in response to the recognition of hyperkalemia. When hyperkalemia is the result of an increase in total body burden of potassium, such as in renal failure, calcium is the treatment of choice. However, calcium administration is not recommended in the setting of digoxin poisoning where extracellular distribution of potassium is the result of a poisoned Na⁺-K⁺-ATPase, not an increase in total body potassium. Under these circumstances, increasing extracellular calcium may accentuate toxicity.

Digoxin-specific Immune Fragments

Administration of digoxin-specific antibody fragments (Fab) is the most important intervention in digoxin-poisoned patients. Fab are prepared by cleaving the Fc fragment from IgG. The resulting Fab fragments are much less immunoreactive than the whole IgG antibodies. In a large series, digoxin-specific
antibody fragments caused allergic reaction in 0.8% of patients (58).

Digoxin-specific Fab should be administered to anyone with
digoxin-induced cardiotoxicity, a serum digoxin concentra-
tion ≥5.0 mg/L after an acute overdose, or a serum digoxin
determination, which is available at some institutions, would not be
dependent on nor await serum digoxin concentration results.
The first clinical effect of Fab should be seen within 20 minutes
and a maximal response within several hours (60). Following
immune-specific antibody fragment administration, the serum
digoxin concentration determined by most laboratories will be
a total digoxin concentration, which will include the antibody-
bound digoxin. The result will be a very elevated value with-
out clinical utility. The determination of free digoxin concentra-
tion, which is available at some institutions, would not be
affected.

β-Adrenergic Antagonists and
Calcium Channel Blockers

The calcium channel blockers (CCBs) are formulated as both
immediate and sustained release, but in overdose, the effects
of either type may be prolonged. The CCBs undergo hepatic
metabolism. There are three major classes of CCBs: Dihydropyridines
(including amlodipine, nifedipine, and others ending with the
suffix “-pine”), phenylalkylamines (verapamil), and benzo-
thiazepine (diltiazem). In practice, it is more clinically useful
to divide them into two classes: the dihydropyridines and the
non-dihydropyridines. All of the drugs inhibit the function of
L-type calcium channels. The dihydropyridines have greater
affinity for calcium channels in vascular smooth muscle than
the myocardium (66).

Clinical Manifestations of Overdose

All β-adrenergic antagonists have the potential to produce
bradycardia and hypotension in a dose-dependent fashion. How-
ever, there are subtle differences among the agents in terms
of receptor selectivity, lipid solubility, membrane-stabilizing ac-
tivity, and potassium channel blockade that result in varied
clinical manifestations.

β-Adrenergic antagonists differ from each other in their se-
lectivity for β1- and β2-adrenergic receptors. Drugs with
α- and β-adrenergic antagonist effects, such as labetalol and
carvedilol, produce more hypotension and afterload reduc-
tion. The more β1-selective drugs, including metoprolol and
atenolol, have less potential for β2-related adverse effects such
as bronchospasm. The more lipid-soluble β-adrenergic antag-
onists, such as propranolol, penetrate the CNS more read-
ily, causing obtundation or seizures prior to hemodynamic
failure. Membrane-stabilizing activity, similar to type 1 antidyssrhythmic activity, produces lengthening of the QRS in-
terval, tachydysrhythmias, and hypotension. The membrane-
stabilizing effect is usually associated with prolongation of the
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Clinical Manifestations of Overdose

The most consequential clinical features of CCB overdose are
cardiovascular. All of the CCBs produce hypotension, but ef-
effects on heart rate and contractility vary based on the class
of the particular drug. As a result, they cause hypotension with
a reflex tachycardia. Diltiazem, in contrast, produces little pe-
nipple blockage, but does suppress contractility and conduc-
tion through the SA and AV nodes, resulting in bradycardia and
degressed myocardy. These cardiac effects can be much

TABLE 66.3
DIGOXIN-SPECIFIC FAB DOSE CALCULATION

<table>
<thead>
<tr>
<th>When serum digoxin concentration (SDC) known:</th>
<th>No. of vials = (SDC (ng/mL) × patient weight (kg))/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>When SDC unknown, dose known:</td>
<td>No. of vials = Amount ingested (mg)/3.5 mg/vial</td>
</tr>
<tr>
<td>When both SDC and dose unknown (acute poisoning)</td>
<td>Empiric therapy</td>
</tr>
<tr>
<td></td>
<td>10–20 vials (adult or pediatric)</td>
</tr>
<tr>
<td>When both SDC and dose unknown (chronic poisoning)</td>
<td>Empiric therapy</td>
</tr>
<tr>
<td></td>
<td>Adult: 3–6 vials</td>
</tr>
<tr>
<td></td>
<td>Pediatric: 1–2 vials</td>
</tr>
</tbody>
</table>

β-adrenergic receptors are coupled to G proteins, which acti-
vate adenyl cyclase, resulting in increased production of ATP
from cyclic adenosine monophosphate (cAMP). The cAMP ac-
vate adenyl cyclase, resulting in increased production of ATP
phosphorylations. Phosphorylation of L-type calcium channels on
Cell membranes increases intracellular calcium, which allows
more activation of the SR and further calcium release from
the SR, causing muscle contraction. The calcium influx also brings
pamemaker cells closer to threshold. The net result is increased
mortality and chronicity (63).

Most of the β-adrenergic antagonists are exclusively me-
tabolized or bio-transformed in the liver and then renally elimi-
nated. The exception to the rule is atenolol, which is exclusively
renally eliminated.

β-Adrenergic Antagonists

<table>
<thead>
<tr>
<th>Adrenergic Antagonists</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
</table>
| β-Adrenergic antagonists and Calcium Channel Blockers | In 2005, the National Poisoning and Exposure Database re-
| | ceived 18,207 reports of exposures to β-adrenergic antagonists
| | (including 60 fatalities and 523 major outcomes) and 10,300
| | reports of exposures to calcium channel blockers (75 fatalities
| | and 384 major outcomes) (6). The β-adrenergic antagonists and calcium channel blockers
| | represent a diverse group of medications with a wide range of
| | clinical indications. There is, however, an overlap in the clinical
effects and the management of overdose of these medications.
| | The description of each class is described individually, whereas
| | the discussion of appropriate management is integrated. |

β-Adrenergic Antagonists

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more difficult to treat than the peripheral vasodilation of the dihydropyridines. In severe poisoning, heart block or complete cardiovascular collapse results. Verapamil, which is active in the peripheral vasculature and in the myocardium, produces a combination of the effects of the dihydropyridines and diltiazem. For this reason, verapamil is considered to be the most dangerous of the CCBs, although any of them can cause death in overdose.

CCBs have effects outside the cardiovascular system. The blockade of L-type calcium channels in pancreatic β-islet cells, where they trigger the blockade of insulin release, may result in hyperglycemia (67).

Management of Overdose of β-adrenergic Antagonists and Calcium Channel Blockers

Patients who initially present without symptoms may rapidly become very ill. Patients with these overdoses should be taken very seriously and treated aggressively. Many antidotes have been investigated, with varying degrees of clinical success. Patients with β-adrenergic antagonist and CCB overdose do not benefit from removal with hemodialysis. There is no single antidote for either β-adrenergic antagonists or CCBs. The optimal treatment consists of a combination of the treatments described below.

Gastrointestinal decontamination should be considered in all patients. Gastric lavage may be indicated if there are pills still expected to be in the stomach (usually in the first hour or two after ingestion). Activated charcoal should be administered. Whole bowel irrigation with polyethylene glycol is indicated for patients with a history of ingesting sustained-release drugs. Initial management for hypotension will be intravenous calcium. Although intravenous atropine, 0.5 mg to 1 mg, may be given for bradycardia, studies of atropine efficacy in CCB toxicity are not definitive (68).

Calcium has a role not only in calcium channel blocker toxicity, but also for β-adrenergic antagonist poisoning (69,70). Increasing extracellular calcium helps to overcome calcium channel blockade and increase intracellular calcium, typically with greater improvement in blood pressure than heart rate. The ideal dosing of calcium is not yet established. An intravenous bolus of 13 to 25 mEq of Ca++ (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate) can be followed by repeat boluses or an infusion of 0.5 mEq/kg/hour of Ca++ (71). Calcium concentration should be closely monitored.

Glucagon, an endogenous polypeptide hormone released by pancreatic α cells, has significant isotropic effects mediated by its ability to activate myocyte adenylate cyclase by itself, effectively bypassing the β-adrenergic receptor (72). Because calcium channel opening occurs “downstream” from adenylate cyclase, glucagon may not be as effective for overcoming calcium channel blockade. Glucagon should be given intravenously, at an initial dose of 3 to 5 mg (30 μg/kg in children), up to 10 mg. The total initial dose that produces a response should be given hourly as an infusion (73). Glucagon may cause hyperglycemia or vomiting, but neither complication should limit the therapy if it is effective.

Hyperinsulinaemia/hyperglycemia therapy should be instituted early in patients with moderate to severe poisoning. Insulin is a positive inotrope and may independently increase Ca++ entry into cells (74). Insulin may allow the myocardium, which usually relies on fatty acids, to use more carbohydrate for metabolism (75). As with other therapies for poisoning with these agents, the ideal dose is not known. We recommend an intravenous bolus of 1 unit/kg, followed by an infusion of 0.5 to 1 unit/kg/hour. The initial bolus should be preceded by a 1 kg bolus of dextrose, followed by an infusion to maintain euglycemia. An initial infusion of 0.5 g/kg/hour of dextrose can be instituted and then adjusted based on the subsequent glucose concentration. Although some clinicians are understandably apprehensive about using a dose of insulin that is 10-fold greater than the typical diabetic ketoacidosis regimen, the regimen has been successfully used clinically and in animal models of both β-adrenergic antagonists and calcium channel blocker poisoning (76,77).

In severe poisoning, all of the above measures should be performed, as well as institution of inotropes and vasoactive drugs. Intra-aortic balloon counterpulsation should also be considered if cardiac output is severely compromised. These patients may be ideal for this procedure because, unlike with most other causes of cardiogenic shock, their cardiac output can recover in a relatively short period of time.

TOXIC ALCOHOLS

The term toxic alcohols refers in particular to methanol and ethylene glycol, which are the most important chemicals in the class because they are both of high potential toxicity and wide availability. In 2005, the NPED received 6,220 reports of exposure to ethylene glycol, including 5.4% classified as major or fatal, and 2.2% exposures to methanol, with 3.2% major or fatal (6).

The toxic alcohols have numerous industrial and consumer uses. Methanol is commonly found in windshield wiper fluid and ethylene glycol in automobile antifreeze, and isopropanol is a ubiquitous topical disinfectant. Since specific laboratory testing is usually not available for these chemicals, establishment of the diagnosis of toxic alcohol poisoning will necessitate skilled use of the serum osmolarity and anion gap.

The toxic alcohols are readily absorbed and have a volume of distribution similar to total body water. Both the parent compounds and the toxic metabolites are dialyzable. It is not the toxic alcohols themselves that produce significant toxicity, but their metabolites. Methanol and ethylene glycol are metabolized in a stepwise fashion by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to the clinically important metabolites formic acid (methanol) and glycolic, glyoxylic, and oxalic acid (ethylene glycol) (Figs. 66.4 and 66.5). Isopropanol is less clinically consequential, as it is converted by ADH to acetone, which is an end product rather than a substrate of ALDH.

Because ADH preferentially metabolizes ethanol over all other alcohols, no significant metabolism of toxic alcohols will occur while high concentrations of ethanol are present. When ADH is inhibited, the parent compounds are eliminated very slowly without metabolism. In the absence of ADH, ethylene glycol is readily eliminated with a half-life of 8.5 hours while methanol, which is eliminated as a vapor, has a half-life of 30 to 54 hours (78–80).

When suspected, toxic alcohol poisoning requires ICU admission. Patients may be obtunded and require therapeutic medication infusions and hemodialysis that cannot be accomplished in general inpatient units.
Clinical Manifestations

The physical examination may be unremarkable. All of the toxic alcohols can produce significant CNS depression, and a compensatory tachypnea may be present if there is a metabolic acidosis. Acetone, generated from ADH metabolism of isopropanol, produces nausea, hypotension, hemorrhagic gastri- tis, and tachycardia, but these are not usually life threatening (81). Formate, a methanol metabolite, can produce blindness from toxicity to the retina and optic nerve (82).

Laboratory studies can suggest—but not establish or exclude—the diagnosis of toxic alcohol poisoning. Metabo- lites of methanol or ethylene glycol may cause an elevated an- ion gap metabolic acidosis. The hallmark laboratory finding of isopropanol poisoning is ketonemia without acidosis. Ethylene glycol may cause nephrotoxicity when the primary metabolite oxalic acid precipitates as calcium oxalate crystals in the renal tubules (83).

Other tests, such as fluorescence of the urine or presence of calcium oxalate crystals in the presence of ethylene glycol pois- oning, are neither sensitive nor specific (85). Since fluorescein is added to some brands of ethylene glycol–based antifreeze in order to facilitate detection of radiator leaks, some authors suggest the use of a Woods lamp to detect urine for fluores- cence as a screen for ethylene glycol. However, in one study of a large group of children not exposed to ethylene glycol, almost all of them had urinary fluorescence (86). Because of the limitations in these laboratory studies, treatment should be started empirically as soon as the diagnosis is considered.

Management

There are several clinical presentations that suggest poisoning with a toxic alcohol, and each requires different management considerations. The first type of patient presents without acidosis and either a history of ingesting ethylene glycol or methanol or a very elevated osmolar gap. The physician should immediately begin an ADH inhibitor and obtain toxic alcohol concen- trations (when available). Later, the decision to continue treat- ment or begin hemodialysis can be made based on the presence of a toxic alcohol in a high concentration. If the result is not expected in a timely manner, dialysis should be presumptively performed.

The second scenario is the patient who presents with an unexplained elevated anion gap metabolic acidosis that is not explained by the presence of lactate, ketoadipic acid, or uremia. In such cases, the diagnosis should be considered, and ADH in- hibition and hemodialysis should be instituted. One test that is very helpful in this scenario is a serum ethanol concentra- tion. As long as there is elevated ethanol concentration present in the serum, toxic alcohols cannot be converted into their metabolites. Therefore, if a patient has a very elevated ethanol concentration, his or her elevated anion gap metabolic acido- sis cannot be explained by toxic alcohol poisoning, unless the ethanol was consumed only hours after the ingestion of the toxic alcohol.

If a serum toxic alcohol concentration is available, the diagnosis can be established rapidly, and management is
CHOLINERGIC COMPOUNDS

Acetylcholine is the neurotransmitter found throughout the parasympathetic nervous system, in the sympathetic nervous system at the level of the ganglia and sweat glands, and at the neuromuscular junction (Fig. 66.6). The cholinergic syndrome describes the condition of excess acetylcholine characterized by the sum of the parasympathetic, somatic, and sympathetic effects. Cholinergic compounds are used as medications, pesticides, and weapons. In 2005, the AAPCC received reports of 42 fatalities and 32 major effects related to organophosphate and carbamate insecticides. The World Health Organization estimates that at least 1 million unintentional poisonings and 2 million suicide attempts occur annually worldwide from these insecticides (88).

Acetylcholine is inactivated in the synapse by acetylcholinesterase (AChE). Inhibition of AChE causes an excess of the neurotransmitter in the synapse. The two most important classes of AChE inhibitors are the carbamates and the organic phosphorous compounds. The carbamates inactivate AChE by carbamylation, while the organic phosphorous compounds do so by phosphorylation. The carbamates and organic phosphorous compounds are both absorbed by ingestion, by inhalation, and through skin.

There are some generalizations that can be made about the two classes. Organic phosphorous compounds have a greater delay to onset of action. After ingestion, peak concentrations have been reported at 6 hours (89). Many of the organic phosphorous agents are activated in the liver, resulting in a further delay to peak action. In contrast, many of the carbamates have peak concentrations within 40 minutes following ingestion (90). The organic phosphorous compounds are generally very lipophilic. Redistribution from far allows measurable serum concentrations for up to 48 days, while carbamates may be almost completely eliminated within days (91,92). Organic phosphorous compounds exhibit peripheral and CNS effects, while the carbamates do not readily cross into the CNS, resulting in a predominance of peripheral symptoms (93). Most importantly, organic phosphorous compounds exhibit “aging,” whereby the reversible inhibition of AChE becomes permanent. Aging can take minutes to days, depending on the particular compound. Carbamates, in contrast, spontaneously hydrolyze from the active site of ACH and do not age. ICU admission is required for those with respiratory compromise, hemodynamic instability, or the need for administration of large amounts of atropine.

Clinical Manifestations

Diagnosis is often established by recognition of the muscarinic signs: salivation, lacrimation, urination, defecation, bradycardia, bronchorrhea, and bronchospasm. Acetylcholine initially acts as an agonist, but in excess becomes an antagonist at the neuromuscular junction, producing weakness, fasciculations, and paralysis. Simulation of nicotinic receptors at the sympathetic ganglia produces tachycardia and mydriasis.

Management

The first management priorities involve securing the airway when necessary and decontaminating the patient’s skin to

Sympathetic

- CNS
  - Confusion
  - Agitation
  - Hallucinations
  - Coma
  - Convulsions

- Adrenal medulla
  - ↑ circulating epinephrine

- Skin (diaphoresis)

- Bronchodilation
- Tachydysrhythmia
- Hypertension
- Urinary retention
- Hyperglycemia

Parasympathetic

- CNS
  - Confusion
  - Agitation
  - Coma
  - Seizures
  - Miosis
  - Lacrimation
  - Salivation
  - Bronchospasm
  - Bradypnoea

- Neuromuscular junction
  - Weakness
  - Fasciculations
  - Paralysis

Somatic

- ACh


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protect caregivers and prevent further absorption. After initial stabilization, atropine should be administered. The presence of tachycardia is not a contraindication to atropine. The goal of “atropinization” is reversal of the muscarinic symptoms. Atropine is titrated to effect the resolution of bronchospasm and bronchosecretion. The initial dose of 1 mg IV atropine (0.05 mg/kg in children) can be doubled every 2 minutes until muscarinic signs are controlled. There is variation in the amount of atropine required, ranging from one to hundreds of milligrams (92).

If CNS anticholinergic toxicity develops prior to resolution of peripheral muscarinic signs, the peripherally acting antimuscarinic agent, glycopyrrolate, may be given, initially at 1 mg IV and then titrated to symptomatic relief. A common clinical pitfall is to interpret froth from the patient’s mouth as a sign of cardiogenic pulmonary edema and respond with fluid restriction. On the contrary, cholinergic-poisoned patients have large volume losses from diaphoresis and bronchosecretion.

Oximes are used to supplement antimuscarinic therapy. The oximes improve both muscarinic and nicotinic signs, primarily by restoring activity to phosphorylated AChE. Since oximes will not restore activity once aging has occurred, they must be administered early in the clinical course of AChE inhibitor poisoning. Oxime therapy is recommended for both organic phosphorous compounds and carbamates because oximes may have salutary effects following carbamate poisoning and because the toxic agent in question is not always known with certainty. Even in carbaryl poisoning, adequate atropinization overcomes any deleterious effect of pralidoxime (94). Pralidoxime (2-PAM) is the oxime most frequently available in the United States. Administer 1 to 2 g IV over 30 minutes (20–40 mg/kg in children, to a maximum of 2 g). Significant poisoning may require a continuous infusion of 500 mg/hour (10–20 mg/kg/hour in children, up to adult dose) (95).

Diazepam should be administered to patients severely poisoned by organic phosphorous compounds. Although human data are not available, animal studies show a survival benefit possibly unrelated to the GABAergic effects of diazepam (96). Because severely poisoned patients will require endotracheal intubation, diazepam can be administered very safely.

Diagnostic Studies

AChe inhibitor poisoning is a clinical diagnosis. Although red blood cell cholinesterase and butyrylcholinesterase are inhibited by carbamates and organic phosphorous compounds, their activity may remain depressed after clinical signs and symptoms have resolved. There may be a clinical role for these tests in mild cases when the diagnosis is unclear. Electromyography (EMG) may be a sensitive indicator of toxicity before clinically apparent symptoms have occurred (97).

Delayed Manifestations

In the acute setting, the physician should be vigilant for recurrence of cholinergic signs after apparent resolution and for a distinct form of toxicity called the intermediate syndrome. The intermediate syndrome—so called because it occurs after acute, but before delayed, toxicity—may occur 24 to 96 hours after organic phosphorous poisoning. The intermediate syndrome consists of upper body weakness, cranial nerve palsies, and areflexia. The syndrome appears to be self-limited,
Cyanide salts are widely available and may be used in suicidal or homicidal poisoning. Because jewelers, laboratory workers, and industrial workers often have ready access to cyanide, a relationship to these industries may be an important historical clue. Cyanide poisoning should also be considered in all fire victims, as it is released when certain synthetic and natural fibers undergo combustion. Cyanide poisoning most frequently occurs after the ingestion of a cyanide salt or inhalation of the gas hydrogen cyanide. In both forms, cyanide is rapidly absorbed. The most important toxic effect of cyanide is inhibition of cytochrome oxidase of the electron transport chain (101). Despite the presence of oxygen, cells cannot oxidize electrons from succinate to generate ATP, resulting in anaerobic metabolism and producing lactic acid. Small quantities of cyanide are detoxified by the enzyme, rhodanese, which catalyzes the transfer of sulfur from thiosulfate, yielding thiocyanate. Poisoning results when this system is overwhelmed by large concentrations of cyanide.

Clinical Manifestations

The history may be very helpful in establishing the diagnosis. Cyanide should be considered in anyone who rapidly loses consciousness after ingestion or inhalational exposure. Signs and symptoms resemble those of hypoxia: headache, lethargy, seizures, and coma in the absence of cyanosis.

Management of Cyanide Poisoning

Cyanide poisoning requires treatment before laboratory confirmation is available, so treatment must be instituted based on clinical suspicion. As soon as cyanide poisoning is considered, 100% oxygen should be administered, intravenous access established, and fluids given. The remainder of treatment depends on the route of exposure. Because the symptoms of cyanide poisoning are similar to those associated with hypovolemia or carbon monoxide poisoning, the diagnosis is difficult to establish with certainty. Laboratory studies will show a lactic acidosis. In one series, a plasma lactate concentration > 8 mmol/L in patients with clinical suspicion of poisoning was 94% sensitive and 70% specific for cyanide toxicity (102).

The cyanide antidote kit consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. Each individual component is beneficial, whereas together they have synergistic activity (103). The nitrites derive their efficacy by generating methemoglobin, which has a greater affinity for cyanide than cytochrome oxidase. When reduced oxygen-carrying capacity is suspected (due to anemia or carboxyhemoglobinemia), the nitrites should be omitted. For this reason, the nitrites should be avoided in patients presenting following smoke inhalation. Such individuals may not tolerate further compromise in their oxygen distribution associated with an increase in methemoglobin.

Amyl nitrite is a volatile liquid. The ampule encasing should be broken and held in front of the patient’s mouth for 1.5-second intervals with 15-second breaks. Once intravenous access is established, sodium nitrite can replace the amyl nitrite. Sodium nitrite is administered 10 mL IV in adults (0.2 mL/kg in children). In 2 hours, the dose can be repeated at half the initial dose (104). A methemoglobin concentration should be obtained 30 minutes after nitrite administration, with a target concentration of 20% to 30%. Sodium thiosulfate, the final component of the kit, functions by providing substrate to rhodanese, facilitating conversion of cyanide to thiocyanate. The dose is 50 mL in adults and 1.65 mL/kg in children, and the drug may be repeated in 2 hours at half the initial dose if symptoms persist. Another potential antidote, hydroxocobalamin, will become available in the United States shortly. Hydroxocobalamin combines with cyanide to form cyanocobalamin (vitamin B₁₂) (105). In animal models, it has synergism with thiosulfate (106). Hydroxocobalamin should be given IV at 70 mg/kg (to a maximum of 5 g) in a separate infusion site from thiosulfate.

Nitroprusside contains an iron molecule coordinated to five cyanide molecules and one molecule of nitric oxide. Cyanide molecules are slowly liberated after nitroprusside is infused, but usually at a rate that can be detoxified by endogenous pathways. Risk factors for accumulation of cyanide are prolonged infusion, high infusion rate, and poor nourishment. If the diagnosis is suspected, the infusion should be discontinued and hydroxocobalamin and thiosulfate administered. A more likely complication of nitroprusside use is thiocyanate toxicity. Thiocyanate, which does not cause any symptoms at low concentrations, is cleared renally. Bioaccumulation occurs in patients with impaired renal function, causing delirium, hallucinations, seizures, and death. In patients receiving >2 μg/kg/min and in those with renal insufficiency, serum thiocyanate concentrations should be checked after 48 to 72 hours of infusion. The infusion should be discontinued if the thiocyanate concentration is >10 mg/dL (107). Dialysis can be effective for thiocyanate accumulation, but should be reserved for only the most severely compromised patients (108).

Methemoglobin

Methemoglobinemia results from the formation of deoxyhemoglobin, which is caused by inappropriate oxidation of heme iron. Under normal conditions, iron in deoxyhemoglobin remains in the reduced ferrous state, Fe²⁺, and the heme is available to bind oxygen. After oxygen binds, iron assumes the oxidized ferric state, Fe³⁺. Methemoglobin, which is normally formed in small quantities, is formed when a hemoglobin iron moiety is exposed to oxidative stress and converted to
the ferric state in the absence of binding oxygen. Methemoglobin is unable to bind oxygen and increases the affinity of normal hemoglobin for oxygen. Thus, the result of methemoglobin formation is decreased oxygen delivery and a leftward shift in the oxygen dissociation curve. Due to the physiologic systems available to reduce methemoglobin to functional hemoglobin, low-level methemoglobin production may be a protective mechanism against oxidant damage to erythrocytes. The most important mechanism of methemoglobin reduction is catalyzed by the enzyme, methemoglobin reductase (cytochrome b_{5}, reductase), using NADH generated from the Embden-Meyerhof glycolytic pathway. Congenital methemoglobinemia is a rare condition caused by methemoglobin reductase deficiency (109). This enzyme is also relatively deficient until approximately 4 months, making infants prone to methemoglobinemia may require ICU admission when it recurs and discharged from the emergency department. Patients with methemoglobinemia may require ICU admission when it recurs following initial treatment, either from continued absorption or deoxyhemoglobin at those wavelengths. When it is present however, has greater absorption than either oxyhemoglobin or deoxyhemoglobin. The pulse oximeter uses an algorithm to estimate the percent-based on the ratio of absorption between the two wavelengths, gives absorbance of light at two wavelengths (660 nm and 940 nm), so chosen because they are the best to distinguish the absorption spectra of oxyhemoglobin and deoxyhemoglobin. Based on the ratio of absorption between the two wavelengths, the pulse oximeter uses an algorithm to estimate the percent-based on the ratio of absorption between the two wavelengths, the pulse oximeter uses an algorithm to estimate the percent-total hemoglobin as oxyhemoglobin. Methemoglobin, the pulse oximeter oxygen saturation (SpO_{2}) to decrease and then plateau at 84% to 86%. In the clinical setting, methemoglobin does not produce this straightforward plateau in SpO_{2}, but does consistently generate readings between 70% and 90% (111). The oxygen saturation derived from the arterial blood gas is not measured in the same fashion as SpO_{2}, and will not reflect the methemoglobin concentration. The oxygen saturation from a blood gas is a calculated saturation based on the pO_{2} and should be normal in the setting of methemoglobinemia. A difference between the SpO_{2} and arterial blood gas-calculated oxygen saturation may suggest methemoglobinemia.

**Clinical Manifestations**

Although the diagnosis of methemoglobinemia is commonly confirmed by co-oximetry, it can be established presumptively based on symptoms and signs, and via pulse oximetry. Symptoms of methemoglobinemia are those associated with hypoxia. The severity of symptoms is determined by the concentration of methemoglobin and the patient’s underlying comorbidities. At low concentrations of methemoglobin (0%–15%), patients may be asymptomatic, and as concentrations rise (20%–50%), patients may manifest decreased exercise tolerance and dyspnea. At higher concentrations (50%–70%), metabolic acidosis, seizures, and coma result. Concentrations greater than 60% or 70% can cause death in previously healthy individuals (111).

Cyanosis is an important physical examination finding that occurs when methemoglobin concentration is 1.5 g/dL. This corresponds to a concentration of 10% in an individual with a total hemoglobin concentration of 15 g/dL. In contrast, 5 g/dL of deoxymethemoglobin is required to produce cyanosis, corresponding to an oxygen saturation of 66% in the same patient. As a result, patients who are cyanotic from methemoglobinemia will not appear as ill as those who are cyanotic from impaired oxygenation. Pulse oximetry aids in diagnosis before co-oximetry has been obtained. Methemoglobin interferes with pulse oximetry in a somewhat predictable manner (112). Pulse oximetry reads absorbance of light at two wavelengths (660 nm and 940 nm), so chosen because they are the best to distinguish the absorption spectra of oxyhemoglobin and deoxymethemoglobin. Based on the ratio of absorption between the two wavelengths, the pulse oximeter uses an algorithm to estimate the percent-total hemoglobin as oxyhemoglobin. Methemoglobin, however, has greater absorption than either oxyhemoglobin or deoxymethemoglobin at those wavelengths. When it is present in modest concentrations, the pulse oximeter will no longer be able to meaningfully calculate oxygen saturation. In a dog model, increasing methemoglobin concentrations caused the pulse oximeter oxygen saturation (SpO_{2}) to decrease and then plateau at 84% to 86%. In the clinical setting, methemoglobin does not produce this straightforward plateau in SpO_{2}, but does consistently generate readings between 70% and 90% (111). The oxygen saturation derived from the arterial blood gas is not measured in the same fashion as SpO_{2}, and will not reflect the methemoglobin concentration. The oxygen saturation from a blood gas is a calculated saturation based on the pO_{2} and should be normal in the setting of methemoglobinemia. A difference between the SpO_{2} and arterial blood gas-calculated oxygen saturation may suggest methemoglobinemia.

**Methemoglobin Inducers**

Acquired methemoglobinemia is most frequently seen after exposure to a drug, although it can also be found in infants without drug exposure who are ill with a metabolic acidosis or diarrhea (113,114). The drugs that have been associated with methemoglobin formation are extensive. Dapsone, nitrites, nitrates, benzocaine, and sulfonamides are consistently implicated in producing methemoglobinemia (115) (Table 66.4).

It is not entirely clear why some individuals develop methemoglobinemia after exposure to these drugs and others do not. Although there is clearly a dose-response effect, host factors such as coexisting medical illness and metabolic variables play a role in methemoglobin development.

**Management of Methemoglobinemia**

When cyanosis is recognized and methemoglobinemia is considered, administer 100% oxygen by nonrebreather mask. Unless the patient is asymptomatic, methylene blue should be administered and given intravenously, 1 to 2 mg/kg over 5 minutes. Methylene blue reduces nicotinamide adenine dinucleotide phosphate (NADPH) to leukomethylene blue. Leukomethylene blue, in turn, reduces methemoglobin to hemoglobin. Clinical improvement should be seen within minutes of administration. Because the medication itself has a blue color, oxygen saturation reported by pulse oximetry may transiently worsen. A repeat dose of methylene blue may be required if the methemoglobin concentration is high or if there is ongoing oxidative stress.

Some authors recommend against giving methylene blue, an oxidizing agent, to individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients with this condition suffer from hemolytic anemia when exposed to drugs that create oxidative stress. Because G6PD is required to activate methylene blue, a deficiency in the enzyme may lead to a lack of efficacy of the antidote. The administration of methylene blue is appropriate when clinically indicated unless there is a strong history of G6PD deficiency. In such cases, hyperbaric oxygen or exchange transfusion should be considered. If the G6PD-deficient patient presents with severe methemoglobinemia, methylene blue should be administered and the patient monitored closely for hemolysis.

**Dapsone-induced Methemoglobinemia**

Both dapsone and its hydroxylamine metabolites are responsible for methemoglobin formation. The cytochrome P450...
Carbon monoxide poisoning does not usually require ICU admission; this is only necessary for patients who are comatose or obtunded, those with signs of cardiotoxicity, and those with significant burns or other comorbidities.

**Clinical Manifestations**

Initially, patients complain of headache, nausea, and dizziness. Because of the vague nature of the complaints, CO poisoning may be misdiagnosed as a viral illness. The diagnosis should be considered when more than one person in a home presents with the same symptoms. Alteration in mental status, coma, seizures, and syncope are signs of severe poisoning. Indicators of tissue hypoxia, such as tachypnea, tachycardia, and ECG changes, may be seen as well. CO can cause dysrhythmias or an acute MI (122); the intensity of signs and symptoms is related to the duration and severity of exposure and comorbid conditions. Pulse oximetry will interpret carboxyhemoglobin as hemoglobin, so the SpO2 will be falsely normal (123). The diagnosis of CO poisoning is aided by obtaining the carboxyhemoglobin concentration, which can be taken from either a venous or arterial sample. The normal carboxyhemoglobin

Conversion of dapsone to these metabolites is inhibited by cimetidine (116). Cimetidine should be administered intravenously, to patients with dapsone-induced methemoglobinemia. Carbon monoxide is a hemotoxin, a neurotoxin, a cardiac toxin, and an inhibitor of cytochrome oxidase. Some of these properties are more important in acute toxicity, while others cause chronic effects. Carbon monoxide binds to hemoglobin with greater affinity than does oxygen, and causes a leftward shift of the oxyhemoglobin dissociation curve, causing a decrease in delivery of oxygen to cells. Although the formation of carboxyhemoglobin can impair oxygen delivery sufficiently to cause mortality, inhibition of oxygen delivery does not fully explain why carboxyhemoglobin concentrations of 50% are often fatal whereas a similar degree of anemia might be well tolerated. The formation of carboxyhemoglobin is inadequate to explain the chronic cardiac and neurologic sequelae of CO. CO inhibition of cytochrome oxidase persists for days after carboxyhemoglobin concentration has normalized (117). CO is associated with damage to the brain endothelium, resulting in lipid peroxidation (118,119). It also binds to myoglobin with high affinity, making it a direct skeletal and cardiac muscle toxin (120).

CO results from the incomplete combustion of carbonaceous fuels. CO is tasteless, odorless, and colorless. The initial clue to the presence of CO in the home may be the alarm from a CO detector. During natural disasters, when electricity is unavailable, people may use generators indoors, allowing CO from exhaust to permeate the home. Even when a home heater is used appropriately, it can lead to CO poisoning if the outflow is obstructed. In automobiles, a functioning catalytic converter minimizes the release of CO. Other internal combustion engines, such as lawnmowers, Zambonis, and outboard motors on boats, do not usually have catalytic converters and can cause CO poisoning. Methylene chloride, an important source of CO that is not a product of combustion, is heparically metabolized to CO by the liver. Methylene chloride is used as a paint stripper and can be absorbed dermally, inhalationally, or by ingestion (121). Unlike other sources of CO poisoning, where carboxyhemoglobin begins to decline as soon as the patient is removed from the exposure, peak carboxyhemoglobin concentration will occur hours after exposure to methylene blue as the parent compound is metabolized to CO.

CO poisoning does not usually require ICU admission; this is only necessary for patients who are comatose or obtunded, those with signs of cardiotoxicity, and those with significant burns or other comorbidities.

**TABLE 66.4**

<table>
<thead>
<tr>
<th>COMMON ETIOLOGIES OF METHEMOGLOBINEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEREDITARY</td>
</tr>
<tr>
<td>Hemoglobin M</td>
</tr>
<tr>
<td>Cytochrome b: reductase deficiency</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ACQUIRED: MEDICATIONS</td>
</tr>
<tr>
<td>Amyl nitrate</td>
</tr>
<tr>
<td>Benzoate</td>
</tr>
<tr>
<td>Dipside</td>
</tr>
<tr>
<td>Lidoacaine</td>
</tr>
<tr>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Nitroprusside</td>
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<tr>
<td>Phenacetin</td>
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<tr>
<td>Phenazopyridine</td>
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<tr>
<td>Phenol</td>
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<tr>
<td>Quinones</td>
</tr>
<tr>
<td>Sulfonamides</td>
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<tr>
<td></td>
</tr>
<tr>
<td>ACQUIRED: OTHER XENOBIOTICS</td>
</tr>
<tr>
<td>Aniline dye derivatives</td>
</tr>
<tr>
<td>Beryl nitrite</td>
</tr>
<tr>
<td>Chlorobenzene</td>
</tr>
<tr>
<td>Fire</td>
</tr>
<tr>
<td>Food adulterated with nitrates</td>
</tr>
<tr>
<td>Food high in nitrates</td>
</tr>
<tr>
<td>Isoamyl nitrite</td>
</tr>
<tr>
<td>Naphthalene</td>
</tr>
<tr>
<td>Nitrite</td>
</tr>
<tr>
<td>Nitrophenol</td>
</tr>
<tr>
<td>Nitrous gases</td>
</tr>
<tr>
<td>Silver nitrate</td>
</tr>
<tr>
<td>Trinitrotoluene</td>
</tr>
<tr>
<td>Well water (nitrates)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PEDIATRIC</td>
</tr>
<tr>
<td>Reduced nicotinamide adenine dimucloride (NADH) methemoglobin reductase activity in infants (&lt;4 mo) associated with low birth weight, prematurity, dehydration, acidosisis, diarrhea, and hyperchloremia</td>
</tr>
</tbody>
</table>

concentration is less than 5%, but smokers may have a concentration of up to 10% (124). Carboxyhemoglobin concentration is an indicator of exposure, but does not correlate with the degree of toxicity (125). When there is a delay from exposure to measurement of carboxyhemoglobin, the concentration loses further value as a clinical tool. This is more likely if the patient has been receiving supplemental oxygen, which decreases the half-life of carboxyhemoglobin.

Chronic Sequelae

For those who survive an acute CO exposure, there may be significant chronic neurologic and cardiovascular effects. Delayed neurologic sequelae (DNS) follow the resolution of initial symptoms, sometimes days to weeks later, and include dementia, movement disorders, and memory impairment (126).

Diagnostic Studies

In patients with chest pain, shortness of breath, palpitations, or neurologic deficits indicating severe exposure, an electrocardiogram should be performed, and serum cardiac markers should be obtained. Pregnancy status should be determined in women of childbearing age.

Elevated serum cardiac markers following moderate and severe acute toxicity predict long-term mortality (127). The pathophysiology of chronic cardiovascular effects of carbon monoxide poisoning probably involves CO poisoning of cardiac myoglobin, but needs further study.

Within 12 hours of exposure, loss of consciousness occurs, and changes on a computed tomography (CT) scan of the brain may be seen. Characteristic findings include symmetric, low-density changes in the globus pallidus, putamen, and caudate nuclei (128). A normal CT scan is a good prognostic indicator. In a series of 18 patients, a negative CT within 1 week of admission was associated with good outcome (129).

Management

As soon as the diagnosis is considered, the patient should be administered 100% oxygen, and the carboxyhemoglobin concentration should be obtained. Without supplemental oxygen, studies have found that the half-life of carboxyhemoglobin in blood is 4 to 6 hours. With oxygen, it has been found to range from 1 to 2 hours (130).

The most important decision is whether to administer hyperbaric oxygen (HBO). While HBO decreases the half-life of carbon monoxide even more rapidly than 100% normobaric oxygen, this is not a clinically important objective. Most patients who are brought to a hospital will survive whether or not they receive HBO. The value of HBO is its potential to decrease morbidity, not mortality. Specifically, HBO may reduce delayed neurologic sequelae. In animal models, HBO prevents brain lipid peroxidation and regenerates CNS cytochrome oxidase after CO exposure (131,132).


All of the trials conducted to date have limitations, and the ideal trial may never be performed because of the ethical concerns of randomizing patients to nonhyperbaric therapy. In light of the demonstrable benefit of HBO and the relative safety of the therapy, we recommend HBO in patients with moderate to severe poisoning. The patient should receive the therapy as early as safely possible; in one series, a delay greater than 6 hours was associated with a worse outcome (133). The following are indications for HBO: (a) syncope, coma, seizure, or any other hard neurologic findings; (b) signs of cardiac ischemia or dysrythmias; and (c) carboxyhemoglobin >20%.

Pregnancy and Carbon Monoxide

Because fetal circulation relies on maternal oxyhemoglobin for oxygenation, any disturbance in maternal oxygen delivery will be magnified in the fetus. Even though fetal hemoglobin has less affinity for CO than adult hemoglobin, there is a high incidence of fetal CNS damage and spontaneous abortion after severe maternal poisoning (134,135). In contrast, pregnant women who have lesser exposures have normal pregnancies and deliver healthy children (136). Because all prospective trials of HBO have excluded pregnant patients, the literature is not clear as to whether this population would benefit from the therapy. We recommend treating these patients similarly to those who are not pregnant.

CAUSTICS

Caustics are chemicals that produce damage during contact with tissues. They are generally acid or alkali, and are commercially available as toilet bowl cleaners, drain cleaners, and other products. There are myriad caustics available in both the home and work environment. Commonly encountered alcalis include ammonium hydroxide (ammonia) and sodium hydroxide (lye, found in drain cleaners). Hydrochloric acid and sulfuric acid are both used as drain cleaners, with the latter used in automobile batteries as well. Alkaline drain cleaners account for more than 3,677 reported exposures each year, more than any other caustic chemical. Of these, 46 were major and 5 fatal (6).

The amount of damage caused by caustics is determined by pH, quantity, duration of contact, and the titratable alkali (or acid) reserve (TAR). Ingested caustics can potentially produce damage to the oropharynx, esophagus, stomach, and respiratory tract. Acid and alkali produce different types of injury. Alkaline exposure produces dissociated OH− ion, resulting in fat saponification, membrane dissolution, and cell death—a process known as liquefactive necrosis (137). Acid exposure releases H+ ions, producing an eschar and desiccation, a process referred to as coagulation necrosis. Both acid and alkali produce stomach and esophageal injury (138).

Esophageal burns can be described by a commonly used classification system (139,140). Grade I burns demonstrate
hyperemia without ulceration; grade II burns demonstrate ulcers, but do not damage periesophageal tissues; grade II lesions are subdivided into IIa (noncircumferential) and IIb (circumferential) lesions; and grade III describes burns with deep ulceration and damage to surrounding tissues. The classification of the burn predicts chronic sequelae: Grade IIb and III injuries may heal with strictures and dysphagia, and may perforate. When esophageal perforation is suspected, or when there is airway injury, patients should be admitted to the ICU.

Clinical Manifestations

The lack of oral burns does not exclude significant esophageal injury, nor does the presence of oral lesions guarantee visceral burns. The physical examination following caustic ingestion can be deceiving. A series of pediatric patients found visceral burns in 37.5% of patients without oral burns and 50% of patients with oral burns (141). Drowning, edynosophagia, and abdominal pain are common findings following significant caustic exposure. However, a series of acid ingestions noted abdominal pain or tenderness in less than half of patients with gastric injury (138).

Pulmonary aspiration may lead to coughing and respiratory distress. Absorption of acid from the stomach may cause acidemia following ingestion. Alkalies are not systemically absorbed in consequential amounts, but a metabolic acidosis may be present if significant injury has occurred.

Management

Esophagoscopy should be performed in all adult patients presumed to have significant exposures in order to establish the severity of the burn. If esophagoscopy is normal, the patient can be safely discharged, while patients with severe injury are rapidly stabilized and referred for surgical care before their condition worsens. Endoscopy should be performed as early as possible, ideally within 12 hours. Wound strength is weakest between 5 days and 2 weeks postingestion, when the perforation risk is greatest. The exception to universal endoscopy may be a subset of pediatric patients based upon a series of 79 patients younger than 20 years of age when no serious esophageal injuries were found in patients who lacked stridor or the combination of vomiting and drooling (142). Another group of investigators found no lesions in asymptomatic pediatric patients (143). The presence of endoscopic evidence of perforation mandates immediate surgery. Other indications for operative repair include pleural effusions, ascites, and a serum pH < 7.2 (144). If endoscopy demonstrates grade I injury, the patient can be started on a soft diet and the diet advanced as tolerated. More severe injury may require parenteral nutrition or a jejunostomy. Silicone rubber esophageal stents have been described (145).

Administer antibiotics that cover anaerobic bacteria and gram-negative aerobic organisms as soon as perforation is considered. Piperacillin/tazobactam are appropriate choices, or levofloxacin and clindamycin. Corticosteroids have been recommended to help prevent scarring and stricture formation in grade II lesions. Randomized controlled trials have provided conflicting results. The most recent meta-analysis could not find a benefit for the administration of corticosteroids following exposure to caustics (146).

HYDROFLUORIC ACID

Hydrofluoric acid (HF) is a weak acid, and does not have important tissue-corrosive properties. HF and ammonium bifluoride have numerous industrial uses. HF dissolves metal oxides and glass, making it useful in rust removal and glass etching. Because of these properties, HF is stored in plastic, not glass. HF is an important dermal, ophthalmic, pulmonary, and systemic toxin. HF penetrates deeply into tissues before disseminating into protons and fluoride ions. Although the protons cause some damage, the most important toxic effects result from fluoride ions binding the divalent cations calcium and magnesium (147). The consumption of these cations leads to neuropathic pain and cell death, HF ingestions and exposures resulting in electrolyte abnormalities require ICU admission.

Clinical Manifestations

HF produces a clinical syndrome distinct from the caustic agents and requires specific therapy. In small dermal exposures, HF produces severe pain with limited dermal findings. Large exposures by any route, including dermal, can produce severe hypocalcemia and death. Most unintentional HF exposures are dermal. The severity of HF exposure is determined by the duration of exposure, concentration, and extent of surface area exposed. Solutions with low fluoride concentration may cause severe pain beginning hours after the exposure, with a very unremarkable physical examination. An area that appears normal or merely mildly erythematous may be extremely painful. High-concentration industrial preparations may cause immediate pain, with hyperemia and ulceration (148). Similarly, ophthalmic exposures result in pain, chemosis, and damage to conjunctiva and corneal epithelium (149).

The most consequential effects of HF poisoning are systemic. Systemic toxicity can result from ingestions or dermal exposures. Dermal exposures to concentrated HF covering as little as 2.5% body surface area have resulted in systemic toxicity, although typical fatal dermal exposures are larger (150,151). Fluoride ions scavenge diveral cations, causing life-threatening hypocalcemia and hypomagnesemia. Hyperkalemia may be seen as well (152). The electrocardiogram may reflect these electrolyte abnormalities. Lengthening of the QRS and QT intervals or presence of peaked T waves may be early indicators of toxicity. The proximal cause of death is usually dysrhythmias; ventricular fibrillation and sudden cardiac arrest have been described (133,154).

Management

The most important concern in small dermal injuries is pain control. The mainstay of therapy is calcium gluconate. The calcium derives its efficacy from binding fluoride ions. Calcium chloride should only be used topically. Should calcium extravasate, the solution itself can cause tissue damage. Other
ANALGESICS and regional anesthesia are not contraindicated, but calcium has the advantage of halting tissue damage in addition to producing pain relief. Following decontamination with water, calcium gluconate gel should be applied to the injured area. If the hands are involved, the gel can be held in contact by placing it in a sterile glove and putting the glove on the hand. Prepare the gel by mixing 25 mL of 10% calcium gluconate in 75 mL of water-based lubricant (155). If the wound is located in an area where compartment syndrome is not a concern, 0.5% calcium gluconate can be injected intradermally, 0.5 mL/cm² (151).

If these techniques fail to give relief, there is a role for careful use of intra-arterial calcium gluconate. The obvious advantage of this route is that calcium can be administered directly and by continuous infusion to the affected area. Add 10 mL of 10% calcium chloride to 40 mL of 0.9% sodium chloride and infuse over 4 hours (156). A nasogastric tube should be carefully placed, and any material in the stomach should be aspirated and followed by instillation of a calcium solution. The benefits of this practice are not established, but it seems reasonable in view of the severity of the ingestion and the relative safety of the intervention.

Intravenous calcium and magnesium should be given liberally, and electrolytes should be obtained hourly. Calcium can be administered as calcium gluconate or calcium chloride. One gram of calcium gluconate contains 4.5 mEq of elemental calcium, and 1 g of calcium chloride contains 13.6 mEq. Both calcium salts can produce vasodilatation and dysrhythmias when administered too quickly. Intravenous calcium should be administered no faster than 0.7 to 1.8 mEq/minute (157). One patient required 267 mEq of calcium over 24 hours (158,159). Dysrhythmias should be expected in severely poisoned patients. Place defibrillator pads on the patient and perform continuous cardiac monitoring. In animal models, quinidine was protective after lethal doses of intravenous fluoride (160). When systemic toxicity occurs, electrolyte abnormalities are most severe in the first several hours of toxicity. Those patients who have no signs or symptoms of systemic toxicity for 24 hours can be transferred to a lower level of care.

**ANTIDIABETIC AGENTS**

Diabetes is characterized by an inability to maintain normal blood glucose concentration due to deficiency of insulin, resistance to insulin, or a combination of both. The medications used to treat diabetes are collectively known as antidiabetic agents, while a subset of these drugs are properly called hypoglycemics. The hypoglycemics include insulin and those drugs that promote the release of endogenous insulin. The terms hypoglycemic agents and antidiabetic agents are not synonymous, because many diabetic medications (metformin, thiazolidinediones) cannot produce hypoglycemia. In 2005, the AAPCC received reports of 8,695 exposures to sulfonyleureas and biguanides, including 244 major exposures and 28 deaths (6).

The antidiabetics are a diverse group of drugs, but some important generalizations can be made. The sulfonyleureas, meglitinides, and thiazolidinediones are very highly protein bound, and thus not amenable to extracorporeal removal. Insulin and metformin are completely renally eliminated, while most of the sulfonyleureas have active hepatic metabolites with urinary excretion of both active metabolites and the parent drug. By far, the most important pharmacokinetic parameter of the hypoglycemics is duration of action. Of great clinical importance, the duration of action of insulin and the sulfonyleureas is greatly increased in overdose. Insulin is available in multiple forms. Short-acting insulin preparations are designed to reduce postprandial hyperglycemia, while long-acting forms are intended to create a constant basal level of insulin. In therapeutic subcutaneous doses, lispro has onset of action within an hour and duration of action of less than 5 hours. Ultralente insulin, the longest-acting insulin commonly used, does not take effect for 4 to 6 hours but lasts as long as 36 hours (161). Regular insulin, lente, and NPH fall in between lispro and ultralente insulin. In overdose, the formation of deposits of the drug in tissues can slow release and greatly prolong the duration of action. The vascularity of the site of injection will also influence the duration of hypoglycemia. The sulfonyleureas generally have a duration of action of 12 to 24 hours in therapeutic doses. Chlorpropamide, a first-generation sulfonyleurea, may promote insulin release for up to 72 hours (162). As in the case of insulin, the duration of action is prolonged in overdose, resulting in delayed hypoglycemia (163). Meglitinides, intended to prevent postprandial hyperglycemia, induce insulin release for only 1 to 4 hours. There is not yet enough data on their pharmacokinetics in overdose, but it appears likely that duration of action would be increased in overdose.

**Clinical Manifestations**

The most important signs and symptoms of the aptly classified hypoglycemics are manifestations of decreased serum glucose. The diagnosis of hypoglycemia is established by interpreting a serum glucose concentration in the context of a patient's clinical status. In one study, the serum glucose threshold for symptoms of hypoglycemia was 78 mg/dL in poorly controlled diabetics and 53 mg/dL in nondiabetics (164). Manifestations of hypoglycemia can be classified as either autonomic or neuroglycopenic. The former result from an increase in counter-regulatory hormones (e.g., epinephrine), while the latter are due to a lack of glucose substrate available for the brain. The autonomic symptoms include tremor, diaphoresis, hunger, and nausea. Neuroglycopenic features of hypoglycemia can manifest as almost any conceivable neurologic deficit, including coma, agitation, seizure, hemiplegia, or mild confusion. Typically, the autonomic symptoms precede neuroglycopenic symptoms, thereby serving as a warning of hypoglycemia before the brain is deprived of a critical level of glucose. However, the autonomic symptoms may be blunted or absent in diabetics or patients taking α-adrenergic antagonists (165). The onset and duration of hypoglycemia is unpredictable after overdose.

Of less clinical importance, the hypoglycemics can also produce electrolyte abnormalities such as hypokalemia, hypomagnesemia, and hypophosphatemia (166). These are reported more frequently in very large insulin overdoses (167).

Metformin does not produce hypoglycemia itself, but is often formulated with drugs that do, such as glipizide or glyburide. Metformin and its biguanide predecessor, phenformin, are associated with lactic acidosis. The biguanides promote anaerobic metabolism and inhibit lactate metabolism (168). Lactic acidosis is rare, but is more likely in the setting of liver disease, renal insufficiency, heart failure, other acute illness,
or acute overdose (169,170). Hepatotoxicity is reported from therapeutic use of thiazolidinediones and acarbose, but there are limited data on acute overdose of these drugs (171,172).

Management

A rapid bedside serum glucose concentration should be obtained as soon as hypoglycemia is considered. If the diagnosis of hypoglycemia is established, 1 g/kg intravenous dextrose should be given. Because high concentrations of dextrose can be irritating, children should receive 25% dextrose solution and infants 10% dextrose solution. As soon as a normal mental status is restored, the patient should be fed. Each 50-mL vial of 50% dextrose supplies 100 kcal of short-lived simple carbohydrate. In contrast, a meal will supply hundreds of “sustained-release” kilocalories. Glucagon should not be administered unless intravenous access is delayed and the patient cannot be fed. Glucagon will not be effective in patients with depleted glycogen stores. If hypoglycemia recurs after it is initially corrected, the treatment is determined by the causative agent. Recurrent insulin-induced hypoglycemia should be treated with a dextrose infusion. Administer a 10% to 20% solution and titrate to maintain glucose in a normal range. A 5% dextrose solution is inappropriate for glucose maintenance.

Octreotide, a somatostatin analogue, is indicated for hypoglycemia following sulfonylurea use. Octreotide should be given subcutaneously, 50 µg every 6 hours (4–5 µg/kg/day in divided doses in children). Dextrose alone might not be sufficient to manage sulfonylurea-induced hypoglycemia. Because sulfonylureas potentiate endogenous β-islet cell insulin release, supplemental dextrose will induce more insulin release, with transient corrections and subsequent recurrence of hypoglycemia. Octreotide inhibits the β-islet cell calcium channel, inhibiting sulfonylurea-induced insulin release (173,174). There are no significant adverse effects of short-term octreotide use. Octreotide should be continued for 24 hours. After octreotide is discontinued, the patient should be observed for 24 hours. There are limited data in the literature regarding meglitinide toxicity. With a mechanism of action similar to the sulfonylureas, the meglitinides are shorter acting. Based on their shorter duration of action, we would expect they would be less likely to produce recurrent hypoglycemia, but we have no data to support this assumption. Until we have more experience with overdose of these drugs, it is prudent to manage meglitinide overdose similarly to sulfonylureas.

Metformin-associated lactic acidosis should be considered in patients taking an overdose of metformin, children exposed to more than one or two tablets, and those patients who take metformin therapeutically who also have renal insufficiency, hepatic insufficiency, heart failure, or another acute illness. The diagnosis is established by obtaining a serum chemistry, lactate concentration, and serum pH. The primary therapy is supportive. Although the role of bicarbonate in metformin-associated lactic acidosis is unclear, supplemental bicarbonate should be used to maintain the pH above 7.1. Although metformin is highly protein bound, hemodialysis can be used to correct refractory acidosis (175).

Adults who present with a history of sulfonylurea overdose and children who may have been exposed to sulfonylureas should be observed for 24 hours, even in the absence of hypoglycemia. Similarly, patients who present with hypoglycemia from long-acting forms of insulin should be observed for 24 hours as well.

NATURAL TOXINS

Plants

This brief discussion focuses on a few important plants that might necessitate intensive care management. In 2005, there were 76 major outcomes resulting from plant exposure that were reported to the AAPCC.

Belladonna Alkaloids

Plants such as jimsonweed (Datura stramonium) contain numerous anticholinergic compounds. They are used recreationally, often in the form of teas, for their hallucinatory effects. Toxicity is identified by the presence of anticholinergic symptoms: tachycardia; hyperthermia; dry, flushed skin; urinary retention; and agitation. One hundred jimsonweed seeds contain nearly 6 mg of atropine and similar alkaloids (176). In addition to supportive care, physostigmine can be given when the diagnosis is relatively certain. Physostigmine is administered 1 to 2 mg IV slowly over 5 minutes. Physostigmine should be discontinued and the diagnosis reconsidered if cholinergic symptoms develop. If there is improvement or no change in the patient’s condition, physostigmine can be readministered after a 10- or 15-minute delay.

Nicotine and Nicotinelike Alkaloids

Nicotine poisoning occurs from inhaled, transdermal, and ingested nicotine. A dose of 1 mg/kg can be lethal in an adult (177). A cigarette contains 13 to 30 mg of nicotine, but most of it is not delivered to the smoker when the cigarette is used as intended. The largest portion of the nicotine is pyrolyzed but not inhaled. As much as 5 to 7 mg of nicotine remains in the cigarette butt, a potentially lethal dose for a child (178). Workers handling tobacco can be poisoned from nicotine as well (179). Signs and symptoms of nicotine toxicity result from activation and then inhibition (from overstimulation) of nicotinic receptors. Gastrointestinal signs include nausea, vomiting, and diarrhea. Early cardiovascular toxicity involves hypertension from nicotinic stimulation of the sympathetic ganglia, but hypotension eventually occurs. The most important signs and symptoms result from nicotinic agonist effects at the neuromuscular junction. Early toxicity causes fasciculation, which gives way to paralysis. Management is supportive. Vasoactive agents may be necessary to maintain blood pressure, and intubation may be indicated to support respiration during paralysis.

Cicutoxin

Cicutoxin is found in Cicuta spp., such as water hemlock. The toxin is found throughout the plant, which is often eaten by adults who misidentify it as wild parsley, turnip, or parsnip (180). The mechanism of cicutoxin poisoning is unclear. Early
symptoms are primarily gastrointestinal and begin soon after ingestion. Later, cicutoxin can cause status epilepticus, renal failure, and rhabdomyolysis (181).

### Sodium Channel–altering Plants

Aconitine, from Aconitum spp., opens sodium channels, increasing cellular excitability (180,182). Increased sodium influx delays repolarization, which in turn delays conduction. Slow conduction of peripheral nerves can lead to decreased sensation, weakness, paralysis, and CNS seizures. Vagal and cardiac myocyte sodium channel effects lead to bradycardia, atrioventricular blockade, increased automatocity, or asystole. Aconitine is found in Aconitum napellus (monkshood) and Chinese herbal remedies. Management is supportive. Gastrointestinal decontamination should be performed. Cardiac complications have been successfully managed with a ventricular assist device (183).

### Mushrooms

Forty-six major outcomes and six deaths from mushroom ingestions were reported to poison control centers in 2005 (6). The vast majority of mushroom exposures do not result in significant morbidity, and most of the fatalities that occur are caused by only a few of the many mushroom species in North America. Identification of mushrooms is challenging and best left to the mycologist. However, because each of the clinically important toxic mushrooms causes a distinct clinical syndrome, the physician should be able to identify the toxicologic manifestations of several mushrooms. Mushroom toxins have been divided into ten groups (184). We will discuss the most common exposures and those most likely to require ICU care.

#### Gastrointestinal Toxin-containing Mushrooms

Most reported exposures are to mushrooms containing gastrointestinal toxins. Hundreds of types of mushrooms fall into this category. The most notable clinical feature of ingestion of these mushrooms is the development of vomiting and diarrhea within several hours of ingestion. With few exceptions, mushrooms that cause gastrointestinal symptoms within 6 hours belong to this category and will not cause life-threatening symptoms. The early onset of vomiting following exposure to gastrointestinal toxin-containing mushrooms clinically differentiates them from the cyclopeptide-containing mushrooms. Treatment of exposure to these mushrooms is supportive, and symptoms are generally self-limited. These mushrooms rarely lead to toxicity requiring ICU admission.

#### Cyclopeptide-containing Mushrooms

Three of the five fatalities from mushrooms in 2004 were related to cyclopeptide-containing mushrooms. Historically, mortality from these mushrooms is high, although improvements in critical care have improved the prognosis. The most prominent member of this group is Amanita phalloides, which contains numerous cyclopeptides, but the most important are a group called the amatoxins. Amatoxins are heat stable and present in lethal concentrations in mushrooms as small as 20 g (184).

Clinical Manifestations and Management. Amatoxins cause endocrine, renal, and CNS injury, but the hepatic effects are the most consequential. Patients will be asymptomatic for the first few hours after ingestion. In 5 to 24 hours, patients will have watery diarrhea. Hepatic toxicity is evident on day 2 with elevations in bilirubin, AST, and ALT. Signs of fulminant hepatic failure such as encephalopathy and coagulopathy follow. Hypoglycemia results not just from hepatic failure, but from direct pancreatic toxicity (185). Cyclopeptides may also cause decreased levels of thyroid hormone and increased calcitonin.

Because patients do not seek help until symptoms develop, it is not uncommon for patients to present to a healthcare facility with volume depletion and early hepatic injury. Good supportive care and prevention of secondary complications are the keys to management. Activated charcoal should be administered 1 g/kg every 2 to 4 hours in order to adsorb any toxin remaining in the gut and interrupt the potential enterohypothalamic circulation (186). Many therapies to mitigate hepatotoxicity have been investigated, with no substantial or reproducible evidence of efficacy.

Although there are no data to support its use in Amanita poisoning, NAC effectively treats hepatic failure from other hepatotoxins, such as acetaminophen. Administer NAC intravenously, according to the acetaminophen protocol: 150 mg/kg over 45 minutes, 30 mg/kg over 4 hours, and 100 mg/kg over 16 hours. Continue the final infusion until the patient expires, definitively recovers, or receives liver transplant.

Silibinin, extracted from milk thistle, improved hepatic markers and mortality in a dog model of Amanita poisoning, but was not found beneficial in a meta-analysis of human studies (187). Because a clinical trial will likely never be conducted, and in light of its experimental benefits, we recommend orally administering silibinin, 20 to 50 mg/kg/day. Silibinin is not a Food and Drug Administration–approved drug, but is available at health food stores.

High-dose penicillin had some effectiveness in a dog model of Amanita poisoning, possibly by blocking hepatic uptake of amatoxin (188). Therapy includes intravenous penicillin G, 1 million units/kg/day in divided doses (189).

The criteria for liver transplantation have not been clearly established. Transplantation is not without risk, and those who survive fulminant hepatic failure from Amanita without transplantation are expected to make a full recovery. Ideally, the decision to transplant should be delayed until it is clear the patient will not recover. Some consider transplantation for those with encephalopathy and prolonged PT, persistent hypoglycemia, metabolic acidosis, increased serum ammonia, aminotransferases, and hypofibrinogenemia (184). Patients should be referred to transplantation centers early in their clinical course so that they may be listed early, and transport should be avoided when they are gravely ill.

#### Gyromitrin-containing Mushrooms

Gyromitrae mushrooms are found throughout the United States. These mushrooms contain gyromitrin (N-methyl-N-formyl hydrazine), which is hydrolyzed to monomethylhydrazine (MMH). MMH inhibits the formation of pyridoxal-5′-phosphate (PLP), an enzyme cofactor synthesized from pyridoxine (vitamin B6). Of great importance, PLP is a cofactor for glutamic acid decarboxylase, the enzyme in the CNS that converts glutamate to GABA. Inhibition of PLP by monomethylhydrazine results in excessive excitation relative to inhibition.
Clinical Manifestations and Management. The initial phase of toxicity, occurring 5 to 10 hours after ingestion, is manifest by numerous clinical features including nausea, vomiting, diarrhea, and headache, and ultimately leads to intractable seizures (184). Patients ingesting Gyromitra spp. should receive activated charcoal, 1 g/kg. Seizures may not respond to benzodiazepines alone. If Gyromitra spp. ingestion is considered, or if a patient presents with seizures after mushroom ingestion, pyridoxine 70 mg/kg IV should be given. Pyridoxine serves as substrate for pyridoxine phosphokinase, allowing some PLP to be generated despite inhibition by MMH.

**Allenic Norleucine-containing Mushrooms**

The nephrotoxic Amanita smithiana contains the amino acid toxins allenic norleucine (amino-hexadienoic acid) and possibly 1,2-amino-8-pentenoyl acid (184). All known exposures to these mushrooms have occurred in the Pacific Northwest of the United States. These serve as important exceptions to the “rule” that mushrooms cause that early gastrointestinal toxicity do not cause significant end-organ damage later.

**Orellanine- and Orellinine-containing Mushrooms**

Cortinarius orellanus, found in North America, contains the toxin orellanine, which is converted by photochemical degradation to another toxin, orellinine (184). Orellanine and orellinine are important causes of mushroom-induced nephrotoxicity. Orellanine is activated by the P450 system. These molecules generate oxidative damage by sustained redox cycling.

Clinical Manifestations and Management. Symptoms begin 24 to 36 hours after ingestion. Patients report headache, chills, polydipsia, nausea, and vomiting. Early laboratory findings of hematuria, leukocyturia, and proteinuria indicate interstitial nephritis. Later, renal failure develops, characterized histologically by tubular damage and fibrosis of tubules with relative glomerular sparing (191, 192). Hepatotoxicity is an uncommon feature.

Management is supportive. Administer activated charcoal if patients present early. Some patients will rapidly improve, whereas others require chronic hemodialysis (193).

**TREATMENT REFUSAL**

Patients with toxicologic emergencies are often suicidal and self-destructive, and may have an altered level of consciousness. We have an ethical obligation to our patients to allow them to make such a decision. The hospital has the right to physically restrain a person who has an altered level of consciousness for the purpose of evaluation and intervention (194).

There is a potential for legal liability whenever the medical staff physically restrain a patient, retain a patient against his or her will, or allow a patient to refuse a life-saving therapy. The physician and hospital staff can reduce liability by thoroughly documenting the patient’s decision-making process and by involving psychiatric consultation in determining the patient’s capacity. When in doubt, the physician should consult the hospital’s legal department.

**OTHER RESOURCES**

This chapter is intended to be a review of common and consequential xenobiotic exposures. Goldfrank’s Toxicologic Emergencies (McGraw-Hill, 2006) contains a more comprehensive review of all the substances discussed here. The regional poison center (1-800-222-1222) is an excellent resource for further information and recommendations specific to your patient.

Owing a great deal to the success of prevention measures, significant poisonings are relatively rare events. In 2005, there were fewer than 20,000 patients with major effects and deaths reported to the AAPCC. Although this figure underestimates total poisoning, it represents a very small number of patients per hospital per year. Because each ICU sees a paucity of these patients, many critical care physicians do not see enough of them to develop familiarity with their care. We encourage close collaboration between ICU physicians, regional poison centers, and toxicologists to provide the best possible care to poisoned patients.

**References**

### SELECTED ANTIDOTES WITH COMMON DOSES

<table>
<thead>
<tr>
<th>Xenobiotic</th>
<th>Antidote and dose</th>
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| Acetaminophen               | N-acetylcysteine: IV: 150 mg/kg infused over 60 min, followed by 50 mg/kg over 4 h, then 100 mg/kg over 16 h  
                           | Oral: 140 mg/kg, followed by 70 mg/kg every 4 h for 17 doses  
                           |                                                                 |
| β-Adrenergic antagonists    | Atropine (for bradycardia): 0.5–1 mg IV  
                           | Glucagon: 3–5 mg IV (50 μg/kg in children) up to 10 mg/h  
                           | Calcium: 13–25 mg/kg of Ca^{2+} IV bolus (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate)  
                           | Hyperinsulinemia/euglycemia: Insulin 0.5–1 U/kg/h accompanied by 0.5 g/kg of dextrose, titrated to maintain euglycemia |
| Calcium channel blockers    | Atropine (for bradycardia): 0.5–1 mg IV  
                           | Glucagon: 3–5 mg/kg (30–60 mL of 10% calcium gluconate)  
                           | Calcium: 13–25 mg/kg of Ca^{2+} IV bolus (10–20 mL of 10% calcium chloride or 30–60 mL of 10% calcium gluconate)  
                           | Hyperinsulinemia/euglycemia: Insulin 0.5–1 U/kg/h accompanied by 0.5 g/kg of dextrose, titrated to maintain euglycemia |
| Cholinergic compounds       | Atropine: 1 mg IV (0.05 mg/kg in children) doubled every 2 min until muscarinic symptoms are controlled  
                           | Pralidoxime: Adults: 1–2 g IV over 30 min followed by 500 mg/m² infusion for sickest patients  
                           | Children: 20–30 mg/kg (max 1–2 g) infused IV over 30–60 min and then 10–20 mg/kg/h (max 500 mg/h)  
                           |                                                                 |
| Cyanide                     | Adults: 1. Sodium nitrite: 300 mg (10 mL of a 3% conc.) infused IV over 2–5 min  
                           | 2. Sodium thiosulfate: 12.5 g (50 mL of a 25% conc.) infused IV over 10–20 min or as a bolus  
                           | 3. Hydroxocobalamin IV 70 mg/kg (up to 5 g)  
                           | Children: 1. Sodium nitrite: 6–8 mL/m² (0.2 mL/kg of a 3% conc., up to adult dose) infused IV over 2–5 min  
                           | 2. Sodium thiosulfate: 7 g/m² (0.5 g/kg, up to adult dose) infused over 10–30 min or as a bolus |
| Cyclic antidepressants      | Sodium bicarbonate: 1 mEq/kg IV bolus, followed by infusion of 150 mEq in 1 L of DSW, infused at twice maintenance rate  
                           |                                                                 |
| Digoxin                     | Digoxin-specific Fab: Known level: 8 of vials = [wt (kg) × level (ng/mL)/100] rounded up to nearest vial. Empiric dosing: Adults: 1 to 2 vials  
                           | Chronic: Adults 3–6 vials; children: 1 to 2 vials. Usually given as IV infusion over 30 min (administer as IV bolus for asystole)  
                           |                                                                 |
| Ethylene glycol, methanol   | Fomepizole: 15 mg/kg infused IV over 30 min; next 4 doses at 10 mg/kg every 12 h; additional doses at 15 mg/kg every 12 h if needed  
                           | Ethanol (when fomepizole not available): 0.8 g/kg infused IV over 20 to 60 min, followed by initial infusion of 100 mg/kg/h  
                           |                                                                 |
| Methemoglobin               | Methylene blue: 1 to 2 mg/kg IV over 5 min followed by a 30 mL fluid flush  
                           |                                                                 |
| Salsylates                  | Sodium bicarbonate: 150 mL in 1 L of DSW, infused at twice maintenance rate. Activated charcoal, 1 g/kg every 4 h  
                           |                                                                 |
| Sulfonylurea-related        | Oxtreotide: 30 μg SQ every 6 h. Children: 1.23 μg/kg (up to adult dose) SQ every 6 h  
                           | hypoglycemia                                                                                                                                          |