Critical Care Neurology

Chapter 49

ANALGESIA AND SEDATION

Pain is a more terrible lord of mankind than even death itself
Albert Schweitzer

Contrary to popular perception, our principal function in patient care is not to save lives (since this is impossible on a consistent basis), but to relieve pain and suffering. And there is no place in the hospital that can match the pain and suffering experienced by patients in the intensive care unit. If you want an idea of how prepared we are to relieve pain and suffering in the ICU, take a look at Figure 49.1.
This chapter focuses on the use of intravenous analgesics and sedatives to achieve patient comfort in the ICU. Several reviews on this topic are included at the end of the chapter (1-5).

PAIN IN THE ICU

Although a majority of ICU patients receive parenteral analgesics routinely (6), 50% of patients discharged from the ICU remember pain as their worst experience while in the ICU (7). This emphasizes the need for effective pain control in the ICU.

Opiophobia

The problem of inadequate pain control is partly due to misconceptions about the addictive potential of opioids, and about the appropriate dose needed to relieve pain (8,9). The following statements are directed at these misconceptions.

Opioid use in hospitalized patients does not cause drug addiction (8).

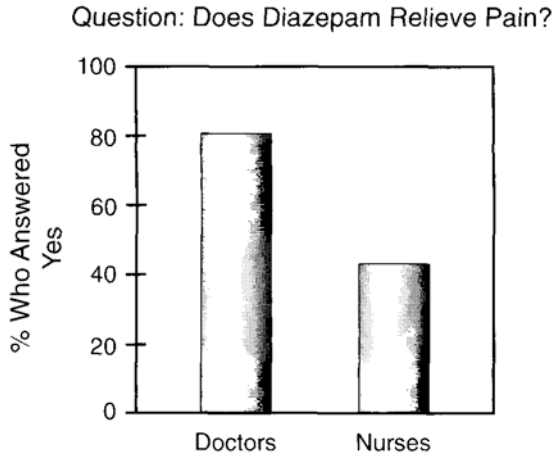

FIGURE 49.1 Percentage of house staff physicians and ICU nurses who answered incorrectly when asked if diazepam (Valium) is an analgesic. (From Loper KA, et al. Paralyzed with pain: the need for education. Pain 1989;37:315.)

The effective dose of an opioid should be determined by patient response and not by some predetermined notion of what an effective dose should be (2).

Avoiding irrational fears about opioids *(opiophobia)* is an important step in providing adequate pain relief for your patients.

Monitoring Pain

Pain is a subjective sensation that can be described in terms of intensity, duration, location, and quality (e.g., sharp, dull). Pain intensity is the parameter most often monitored because it best reflects the degree of discomfort. The intensity of pain can be recorded using a variety of scales like the ones shown in Figure 49.2. The uppermost scale (Adjective Rating Scale) uses descriptive terms, the middle scale (Numerical Ranking Scale) uses whole numbers, and the lower scale (Visual Analog Scale) records pain intensity as a discrete point placed along a line between the ends of the pain intensity spectrum.

Pain intensity scales can be used to evaluate the effect of analgesic regimens in individual patients. A numerical score of 3 or less on the Numerical Rating Scale or Visual Analog Scale can be used as evidence of effective analgesia. However, it seems easier to just ask patients if their pain is well controlled. Direct communication with patients is not only the best method of determining comfort needs, it is itself a source of comfort to patients. When critically **ill** patients are unable to communicate directly about pain intensity, the use of surrogate signs of pain such as physiological parameters (e.g., heart rate) or elicited behaviors (e.g., facial expressions) is an unproven and probably inappropriate practice (2,10).

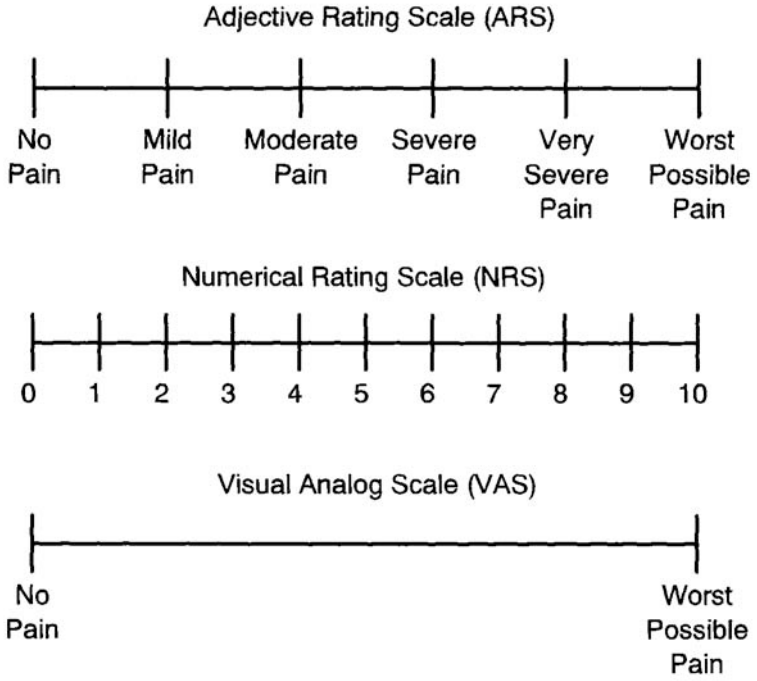

FIGURE 49.2 Three different scales for recording pain intensity. The recommended length for the numeric scales (NRS and VAS) is 10 cm. (For more information on recording pain intensity, see Hamill-Ruth RJ, Marohn ML. Evaluation of pain in the critically ill patient. Crit Care Clin 1999;15: 35.)

OPIOID ANALGESIA

The natural chemical derivatives of opium are called *opiates.* Opiates and other substances that produce their effects by stimulating discrete opioid receptors in the central nervous system are called *opioids.* Stimulation of opioid receptors produces a variety of effects, including analgesia, sedation, euphoria, pupillary constriction, respiratory depression, bradycardia, constipation, nausea, vomiting, urinary retention, and pruritis (11). *Narcotic* (from the Greek *narkotikos,* to benumb) refers to the general class of drugs that blunt sensation and produce euphoria, stupor, or coma.

Opioids are the agents most frequently used for pain relief *and* mild sedation in the ICU (5,6,12). They are most effective for relieving dull tonic pain, less effective for intermittent sharp pain, and relatively ineffective for neuropathic pain. Although opioids cause mild sedation, they do not cause amnesia (unless the patient goes to sleep!) (3).

Intravenous Opioids

The opioids used most often in the ICU are morphine, fentanyl, and hydromorphone (5,6,12). The intravenous administration of these agents

TABLE 49.1 Intravenous Opioid Analgesia

	Morphine	Hydromorphone	Fentanyl
Loading dose	5-10 mg	1-1.5 mg	50-100 μg
Onset of action	10-20 min	5-15 min	1-2 min
Duration (after bolus)	2-3.5 hrs	2-3 hrs	30-60 min
Infusion rate*	1-5 mg/hr	0.2-0.5 mg/hr	50-350 μg/hr
PCA			
demand (bolus)	0.5-3 mg	0.1-0.5 mg	15-75 μg
lockout interval	10-20 min	5-15 min	3-10 min
Potency	x	5x	100x
Lipid solubility	x	0.2x	600x
Active metabolites	Yes	Yes	No
Histamine release	Yes	No	No
Dose adjustment for GFR <10 mUmin	Decrease by 50%	None	Decrease by 0-50%
Cost per 24 hrs[t]	5 mg/hr: $16	0.75 mg/hr: $10	100 μg/hr: $5.50

*Initial infusion rate. May need further adjustment.
tBased on average wholesale price in
Adapted from References 1, 2, 14-16.

is described in Table 49.1. The doses shown in this table are the usual effective doses, but individual dose requirements can vary widely. Remember that the effective dose of an opioid is determined by each patient's response, not by the numeric value of the dose (2,16). Continued pain relief often requires continued drug administration, either as a continuous infusion or by regularly scheduled drug dosages. Intermittent, as-needed (PRN) drug administration is a recipe for inadequate pain control and is never recommended 0,2).

Fentanyl versus Morphine

Morphine is the most frequently used opioid in ICUs (2), but fentanyl may be preferred because it is faster acting, devoid of active metabolites, and less likely to decrease blood pressure. Because fentanyl is 600 times more lipid soluble than morphine, it is taken up much more readily into the central nervous system. The result is a quicker onset of action and equivalent analgesia at a fraction (1/100) of the dose of morphine.

Opioids are metabolized primarily in the liver, and the metabolites are excreted in the urine. Morphine has several active metabolites that can accumulate in renal failure. One metabolite (morphine-3-glucuronide) can produce central nervous system excitation with myoclonus and seizures (7), while another metabolite (morphine-6-glucuronide) has more analgesic effect than the parent drug (1). To avoid accumulation of these metabolites, the maintenance dose of morphine should be reduced by 50% in patients with renal failure 05). Fentanyl does not have active metabolites, and dose not need dose adjustments in renal failure.

Morphine promotes the release of histamine, which can cause vasodilation and hypotension (8). Fentanyl is devoid of this effect (8), and thus **fentanyl is preferred to morphine for patients with hemodynamic compromise**. Fentanyl also has a faster onset of action, which allows more rapid dose titration.

CAVEAT. Infusions of fentanyl lasting longer than 4 hours can produce prolonged drug effects as a result of drug accumulation in fatty tissue. This effect can be minimized by titrating the dose down to the lowest possible dose that relieves pain.

Patient-Controlled Analgesia

For patients who are awake and capable of drug self-administration, *patient-controlled analgesia* (PCA) can be an effective method of pain control. The PCA method uses an electronic infusion pump that can be activated by the patient. When pain is sensed, the patient presses a button connected to the pump to receive a small intravenous bolus of dmg. After each bolus, the pump is disabled for a mandatory time period called the *lockout interval,* to prevent overdosing. The recommended dose regimens for PCA are shown in Table 49.1. The minimum lockout interval is determined by the time required to achieve peak drug effect (4). When writing orders for PCA, you must specify the initial loading dose (if any), the lockout interval, and the repeat bolus dose. PCA can be used alone or in conjunction with a low-dose opioid infusion.

PCA is associated with more effective analgesia, improved patient satisfaction, and fewer side effects than traditional intermittent opioid administration. Use of background opioid infusion increases the risk of respiratory depression, especially when combined with sedative drugs.

Epidural Opioids

Epidural instillation of opioids is a popular method of pain control following thoracic and abdominal surgery. Epidural catheters are usually placed in the operating room, just before surgery, and are left in place for the first few postoperative days. Drugs administered through the catheter produce a band-like distribution of analgesia extending several derma tomes above and below the catheter tip. Typical dose regimens for epidural analgesia are shown in Table 49.2. Epidural opioids can be given as intermittent boluses, but are more often given as a continuous infusion along with a local anesthetic such as bupivacaine. Adding a local anesthetic increases the analgesic effect of epidural opioids (synergistic effect) and reduces the risk of opioid side effects (20). Epidural instillation of local anesthetics can cause motor weakness and hypotension, and dilute drug solutions are used to avoid these side effects.

Therapeutic and Adverse Effects

Clinical studies comparing epidural and systemic opioid analgesia have been inconsistent, but the general impression is that epidural analgesia is associated with improved analgesia, faster recovery of bowel function, fewer

TABLE 49.2 Epidural Analgesia

Agent	Concentration
Opioids	
Fentanyl	2-5 μg/mL
Morphine	20-100 μg/mL
Dilaudid	0.04 mg/mL
Local Anesthetics	
Bupivacaine	0.06-0.125% (0.6-1.25 mg/mL)
Ropivacaine	0.1-0.2% (1-2 mg/mL)

Note:
1) Typical starting infusion rates are 4 to 8 mUhr for thoracic epidural and 6 to for lumbar epidural. Dilute solutions of opioids and local anesthetics should be initially for patient age 2:65 yrs.
2) Prolonged infusion of local anesthetics at higher dose ranges can cause lower extremity weakness, and urinary retention.
Adapted from Reference 20.

pulmonary complications, and a decreased risk of myocardial infarction (20,21). Epidural analgesia does not reduce postoperative mortality (20). Adverse effects of epidural analgesia are more common with morphine than fentanyl. Epidural morphine can produce respiratory depression, and the onset can be delayed up to 12 hours (22). *The incidence of respiratory depression is equivalent with epidural and intravenous morphine (1 % and 0.9%, respectively*) (20). More frequent side effects of epidural analgesia include pruritis (28-100%), nausea (30-100%), and urinary retention 05-90%) (20). The pruritis from epidural opioids can be treated as described in the next section.

Adverse Effects of Opioids

There is a long list of adverse reactions to opioids; the following ones are of particular concern in the ICU. (For a comprehensive review of opioid side effects, see references 22-24.)

Respiratory Depression

Opioids produce a centrally mediated, dose-dependent decrease in both respiratory rate and tidal volume (23,25), but respiratory depression and hypoxemia are uncommon when opioids are used judiciously (26). High doses of opioids can produce apnea, an effect mediated by peripheral opioid receptors located in the lungs (23). When opioids cause difficulty in arousal, there is almost always an associated respiratory depression with hypercapnia (22). Patients with sleep apnea syndrome or chronic hypercapnia are particularly prone to respiratory depression from opioids, especially when opioids are combined with other respiratory depressant drugs (24).

Cardiovascular Effects
Opioid analgesia is often accompanied by decreases in blood pressure and heart rate, which are the result of decreased sympathetic activity and increased parasympathetic activity. These effects are usually mild and well tolerated, at least in the supine position (24). Decreases in blood pressure can be pronounced in patients with hypovolemia or heart failure (where there is an increased baseline sympathetic tone), or when opioids are given in combination with benzodiazepines (27). Opioidinduced hypotension usually responds to intravenous fluids or small bolus doses of vasopressors.

Intestinal Motility
Opioids are well known for their ability to depress bowel motility, and this effect can be prominent in ICU patients. Oral naloxone in a dose of 4 to 8 mg every 6 hours can antagonize opioid-induced bowel hypomotility without antagonizing the systemic analgesic effect (28). Higher doses will produce systemic opioid antagonism and should be avoided.

Pruritis
A generalized pruritis is reported in 30 to 100% of patients receiving epidural opioids, and in fewer than 10% of patients receiving intravenous opioids (20,28). Symptoms are usually not relieved by antihistamines, but they can be abolished by a low-dose naloxone infusion (0.25-1 μg/ kg/hr) without loss of analgesic effects (28).

Nausea and Vomiting
Opioids can promote vomiting via stimulation of the chemoreceptor trigger zone in the lower brainstem (23). All opioids are equivalent in their ability to promote vomiting, but when one agent provokes vomiting, switching to another opioid can sometime provide symptom relief. Antiemetic agents (e.g., ondansetron) and low doses of opioid antagonists can also produce effective symptom relief.

Meperidine
Meperidine (Demerol, Pethidine) is a popular opioid analgesic that can be an excitatory neurotoxin in critically ill patients. Meperidine is metabolized in the liver to form normeperidine, a metabolite that is slowly excreted by the kidneys (elimination half-life is 15-40 hours) (29). Accumulation of normeperidine can produce central nervous system excitation with agitation, tremors, myoclonus, delirium, hallucinations, and tonic-clonic seizures (29). Normeperidine can accumulate with repeated doses of meperidine, and the accumulation is more pronounced when renal function is impaired. Since ICU patients often have impaired renal function, the risk for neurotoxicity from accumulation of normeperidine is high in this patient population.

Because of the risk for neurotoxicity in critically **ill** patients, meperidine is not advised for pain control in ICU patients. The traditional belief that meperidine is the preferred opioid for pain relief in cholecystitis and pancreatitis is contrary to experimental studies showing that meperidine and morphine are equivalent in their ability to promote spasm of the sphincter of Oddi and increased intrabiliary pressure (29,30). Nonsteroidal antiinflammatory drugs like ketorolac (see later) do not increase intrabiliary pressure (31), and these agents should be used when possible for pancreaticobiliary pain.
Although not advised as an analgesic in the ICU, meperidine continues to be the preferred agent for control of shivering. In postoperative patients, low doses of meperidine (25 mg IV) usually stop shivering due to hypothermia within 5 minutes.

NONOPIOID ANALGESIA
There are few alternatives to the opioids for providing effective analgesia via the parenteral route. In fact, there is only one alternative agent approved for use in the United States: ketorolac.

Ketorolac
Ketorolac is a nonsteroidal antiinflammatory drug (NSAID) introduced in 1990 as a parenteral analgesic for postoperative pain (32, 33). Because ketorolac does not cause sedation or respiratory depression, it was greeted with enthusiasm (34), but its popularity has waned because of the risk for other troublesome side effects.

Analgesic Effects
Ketorolac is a nonspecific inhibitor of cyclooxygenase with strong analgesic activity and moderate antiinflammatory activity (33). On an equal weight basis, it is 350 times more potent than aspirin (33). After intramuscular OM) injection of ketorolac, analgesia is evident at 1 hour, peaks at 2 hours, and lasts 5-6 hours. The drug is partly metabolized in the liver and excreted in the urine. Elimination is prolonged in renal impairment and old age.
For postoperative analgesia, 30 mg ketorolac 1M is equivalent to 10 to 12 mg morphine 1M (32). Ketorolac can be given alone, but is often given with an opioid. It has an *opioid sparing effect,* and the opioid dose can often be reduced by 25-50% (32).

Dosing Regimen
Ketorolac can be given orally, intravenously, or by 1M injection. For patients under 65 years of age, the initial dose is 30 mg IV or 60 mg 1M, followed by 30 mg 1M or IV every 6 hours (maximum of 120 *mgl* day) for up to 5 days. For patients >65 years of age, under 50 kg, or with renal dysfunction, the initial dose is 15 mg IV or 30 mg 1M, followed by

15 mg 1M or IV every 6 hours (maximum of 60 mg/ day) for up to 5 days. Because 1M injection of ketorolac can cause hematoma formation, IV bolus injection is preferred (35). Ketorolac has also been given by continuous IV infusion (5 mg/hr), resulting in more effective analgesia than intermittent IV doses (35).

Adverse Effects

Like other NSAIDs, ketorolac inhibits platelet aggregation, and it should not be used in patients with a high risk of bleeding (34). When ketorolac is given for more than 5 days, and in doses exceeding 75 mg/ day, there is an increased risk of gastrointestinal and operative site bleeding (36). The risk of bleeding is greatest for patients over 65 years old. Ketorolac inhibits renal prostaglandin synthesis and may impair renal function, but the risk of renal toxicity is minimal if drug therapy does not exceed 5 days.

ANXIETY IN THE ICU

Anxiety and related disorders (agitation and delirium) are evident in as many as 85% of patients in the ICU (37). The common denominator in these conditions is the *absence of a sense of well-being.* Anxiety is characterized by exaggerated feelings of fear, nervousness, or apprehension that are sustained more by internal than external events. Agitation is a combination of anxiety and increased motor activity. Delirium is a specific syndrome of altered mental status that mayor may not have anxiety as a component. Although delirium is often equated with agitation, there is a hypoactive form of delirium that is characterized by lethargy. The anxiety disorders are described in more detail in Chapter 50.

Sedation

Sedation is *the process of establishing a state of calm.* Talking to patients and making adjustments in the ICU environment should be the first steps to calm an anxious patient. In the ICU, however, drugs are often needed to calm patients, and as many as 22 different medications are used for this purpose (5). The agents most frequently used are midazolam, propofol, lorazepam, and opioid analgesics (5,6,12).

Monitoring Sedation

Current guidelines recommend routine monitoring of sedation 0), and the use of protocols to guide sedation can decrease the time spent on mechanical ventilation by as much as 50% (38). A number of scoring systems are available for this purpose, but no system has been fully validated (39). Each system evaluates consciousness first by noting spontaneous responsiveness to the observer, and subsequently (if necessary) by noting responses to graded levels of external stimulation (voice or touch). Sedation scores are not intended for patients who are unconscious or receiving a neuromuscular blocking agent.

TABLE 49.3 Ramsay Scale for Scoring Sedation

	Modified Ramsay Scale
Score	Description
1	Anxious and agitated or restless, or both
2	Cooperative, orientated, and tranquil
3	Drowsy, but responds to commands
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep and unarousable

Adapted from Reference 39.

The Ramsay scale (see Table 49.3), described in 1974, was the first scoring system for evaluating sedation in mechanically ventilated patients (40). This scale is designed to monitor the level of consciousness more than the degree of agitation because it distinguishes four levels of sedation (score 3 to 6), but only one level of agitation (score = 1). Despite this shortcoming, and a lack of scientific validation, the Ramsay scale is the chosen method of monitoring sedation in more than 75% of ICUs (2).
Other sedation scales are included in the Appendix. The sedationanalgesia scale (SAS) distinguishes three different levels of agitation (41), and the Richmond Agitation Sedation Scale (RASS) offers the advantage of following changes in the level of sedation on consecutive days (42).
The goal of sedation in the ICU is a patient who is calm but easily arousable. The use of a sedation scale will allow you to achieve and maintain this goal with the lowest possible dose of a sedative agent and with the lowest possible risk of harm to your patient.

SEDATION WITH BENZODIAZEPINES

Benzodiazepines are popular sedatives in the ICU because they are generally safe to use, and the sedation is accompanied by amnesia. Of the 13 benzodiazepines available for clinical use, 3 can be given intravenously: midazolam, lorazepam, and diazepam. Table 49.4 presents some pertinent information on the intravenous benzodiazepines, and the following statements summarize some characteristic features of benzodiazepines.
All are lipid soluble to some degree, metabolized in the liver, and excreted in the urine.
Therapeutic doses of benzodiazepines do not cause respiratory depression in healthy subjects, but this effect can occur in select ICU patients (e.g., those with respiratory insufficiency) (44).
The dose of benzodiazepines needed to achieve adequate sedation is lower in elderly patients (45), and in patients with heart failure and hepatic insufficiency, due to a slowing of benzodiazepine metabolism.

TABLE 49.4 Sedation with Intravenous Benzodiazepines

	Midazolam	Lorazepam[1]	Diazepam[2]
Loading dose (IV)	0.02-0.1 mg/kg	0.02-0.06 mg/kg	0.OS-0.2 mg/kg
Onset of action	1-5 min	5-20 min	2-5 min
Duration (after bolus)	1-2 hr	2-6 hr	2-4 hr
Maintenance infusion	0.04-0.2 mg/kg/hr	0.01-0.1 mg/kg/hr	Rarely used
Potency	3x	6x	x
Lipid solubility	1.5x	0.5x	x
Active metabolites	Yes	No	Yes
Dose adjustment for GFR <10 mUmin	Decrease 0-50%	None	None
Cost per 24 hours	4 mg/hr: $37	2 mg/hr: $52	8 mg q 4 h: $24

1 Lorazepam: 2 mg/mL (Abbott Labs, Chicago, IL) contains propylene glycol as solvent
2 Diazepam:10 mg/2 mL (Abbott Labs, Chicago, IL) contains propylene glycol (400 mg/mL) as solvent
Adapted from References 1, 3, 15, 43-45,

Even though the elimination half-life of diazepam is 20 to 50 hours versus 2 to 8 hours for midazolam, the clinical recovery time is the same following a single intravenous dose of each drug (46). This discrepancy is explained by the relatively rapid uptake of diazepam from plasma into fatty tissues. Avid uptake by fat is also observed with lorazepam.
When an overdose of lorazepam or diazepam is given, the clinical recovery time until the patient is fully awake may be prolonged as a result of drug accumulation.

Drug Comparisons
Midazolam (Versed) is the benzodiazepine of choice for short-term sedation because it has the highest lipid solubility, the fastest onset, and the shortest duration of action of all the intravenous benzodiazepines (43-45). Because of its short duration of action, midazolam is commonly given by continuous infusion. Infusions of midazolam lasting more than a few hours can produce prolonged sedation after the drug infusion is stopped. This effects is the result of multiple factors, including (a) drug accumulation in the central nervous system, (b) accumulation of an active metabolite (hydroxymidazolam), especially in renal failure, (c) inhibition of cytochrome P450 (involved in midazolam metabolism) by other medications (Table 49.5), and (4) hepatic insufficiency 0,43,49). To reduce the risk for oversedation, the infusion rate of midazolam should be determined using ideal body weight rather than total body weight (43).
Lorazepam (Ativan) has the slowest onset of action of the intravenous benzodiazepines. Because of its long duration of action, lorazepam

TABLE 49.5 Drug Interactions with Benzodiazepines

Drugs	Mechanism	Significance	Recommendations
Interactions that ENHANCE Benzodiazepine Efficacy			
Fluconazole Erythromycin Clarithromycin Diltiazem Verapamil Rifampin Cimetidine Disulfiram Omeprazole	Inhibit cytochrome P-450 to slow hepatic metabolism of diazepam and midazolam.	Interaction between midazolam and erythromycin may be most significant.	Avoid drug combination, or reduce benzodiazepine dose as needed.
Interactions that REDUCE Benzodiazepine Efficacy			
Rifampin	increased diazepam and midazolam.	Significance unclear.	Dosage adjustment when clinically indicated.
Theophylline	Antagonizes benzodiazepine actions by adenosine inhibition.	Significant interaction.	Avoid theophylline.

Adapted from References 43, 47, 48.

is best suited for patients who require prolonged sedation (e.g., ventilator-dependent patients) 0). Lorazepam should not be used when rapid awakening is desired (45).

Diazepam (Valium) is the least favored of the intravenous benzodiazepines because of the risk for oversedation with repeated drug administration. Continuous infusions of diazepam should be avoided because of the risk for prolonged sedation caused by accumulation of parent drug and its active hepatic metabolites (3).

Toxic Effects

Excessive dosing of benzodiazepines can produce hypotension, respiratory depression, and excessive sedation (50). The manifestations and treatment of benzodiazepine toxicity are described in Chapter 53.

Propylene Glycol Toxicity

Intravenous preparations of lorazepam and diazepam contain the solvent propylene glycol to enhance drug solubility in plasma. This solvent can cause local irritation to veins, which is minimized by injecting the drug into a large vein. A bolus of propylene glycol can cause hypotension and bradycardia, and prolonged administration of propylene glycol can cause paradoxical agitation, metabolic acidosis, and a clinical syndrome

that mimics severe sepsis. Propylene glycol toxicity is described in more detail in Chapter 29. When propylene glycol toxicity is suspected, it is wise to change to midazolam or propofol for sedation because these drug preparations do not contain this solvent.

Withdrawal Syndrome
Abrupt termination following prolonged benzodiazepine administration can produce a withdrawal syndrome consisting of anxiety, agitation, disorientation, hypertension, tachycardia, hallucinations, and seizures (49). Benzodiazepine withdrawal can also be a cause of unexplained delirium in the first few days after ICU admission (51). The risk of withdrawal is difficult to predict. For patients maintained for several days on a midazolam infusion, transitioning to propofol (mean dose 1.5 mg/kg/hr) 1 day prior to planned tracheal extubation can decrease the incidence of agitation observed after patient extubation (52).

Drug Interactions
Several drugs interfere with hepatic oxidative metabolism of diazepam and midazolam; these are listed in Table 49.5. These interactions do not apply to lorazepam, which is metabolized by glucuronidation (47). The interaction between theophylline and benzodiazepines also deserves mention. Theophylline antagonizes benzodiazepine sedation possibly by inhibiting adenosine, and intravenous aminophylline (110 mg over 5 minutes) has been reported to cause more rapid awakening from benzodiazepine sedation in postoperative patients (48).

OTHER SEDATIVES

Propofol
Propofol (Deprivan) is a rapidly acting sedative agent that is used for induction and maintenance of anesthesia and short-term sedation (<72 hrs). The use of this drug in the ICU should be limited by the risk for adverse reactions (particularly hypotension).

Actions and Uses
Propofol causes sedation and amnesia but has no analgesic activity (53). A single intravenous bolus of propofol produces sedation within 1 minute, and the drug effect lasts 5-8 minutes (53). The properties of this drug are shown in Table 49.6. Due to its short duration of action, propofol is given as a continuous infusion. After discontinuing a propofol infusion, awakening occurs within 10-15 minutes, even after prolonged administration (53).
Propofol can be used for short-term sedation when rapid awakening is desired (e.g., during brief procedures), or during transition from a long-acting sedative during patient recovery (52). Propofol can be useful in neurologic injury because it reduces cerebral oxygen consumption and intracranial pressure (53). Other conditions where propofol has been used include refractory status epilepticus (54) and delirium tremens (55).

TABLE 49.6 Sedation with Alternate Intravenous Agents

	Propofol	Dexmedetomidine
Loading dose	0.25-1 mg/kg	1 μg/kg over 10 min
Onset of action	<1 min	1-3 min
Time to arousal	10-15 min	6-10 min
Maintenance infusion	25-75 μg/kg/min	0.2-0.7 μg/kg/hr
Active metabolites	No	No
Respiratory depression	Yes	No
Side effects	Hypotension	Hypotension
	Hyperlipidemia	Bradycardia
	Contamination/Sepsis	Sympathetic
	Rhabdomyolysis	after >24 hr infusion
	Propofol Infusion Syndrome	
Cost per 24 hrs*	30 μ/kg/min: $303	0.3 μg/kg/hr: $214

*Cost for 70 kg person based on average wholesale price
Adapted from References 1, 4, 53.

Preparation and Dosage
Propofol is very lipid soluble, and the drug is suspended in a 10% lipid emulsion to enhance solubility in plasma. This lipid emulsion is almost identical to 10% Intralipid used in parenteral nutrition formulas, and the nutritive content of the emulsion (0.1 mg fat/ml or 1.1 kcal/ml) should be counted as part of the daily nutrient intake. Propofol is dosed based on ideal rather than actual body weight, and no dose adjustment is required for renal failure or moderate hepatic insufficiency (53).

Adverse Effects
Propofol is well known for producing pain on injection, respiratory depression, apnea, and hypotension (53). Because of the risk of respiratory depression, infusions of the drug should be used only in patients on controlled ventilation. Decreased blood pressure is frequently observed following a bolus dose of propofol, and significant hypotension is most likely to occur in patients who are elderly or have heart failure (53). Hemorrhagic shock greatly enhances the hypotensive effects of propofol, even after resuscitation with intravenous fluids (56). Propofol should be avoided in patients with hemorrhagic shock. Anaphylactoid reactions to propofol are uncommon but can be severe (53), and green urine is observed occasionally as a result of clinically insignificant phenolic metabolites (53)

The lipid emulsion in commercial propofol preparations can be a source of unwanted side effects. Hypertriglyceridemia occurs in up to 10% of patients receiving propofol, especially after 3 days of continuous infusion (57). Serum triglyceride levels should therefore be monitored

during prolonged propofol infusions. The lipid emulsion also promotes bacterial growth (53), and improper sterile technique when giving propofol has resulted in an epidemic of hyperthermic reactions and postsurgical wound infections (58). To suppress microbial growth, commercial preparations of propofol contain either disodium edetate (EDTA, AstraZeneca) or sodium metabisulfite (Baxter). EDTA chelates zinc, and zinc supplementation should be considered for propofol infusions lasting longer than 5 days. Allergic reactions to the sulfite preservative are rare but are more common in patients with a history of asthma (1).

Bradycardia-Acidosis (Propofol Infusion Syndrome) is a rare and often lethal idiosyncratic reaction characterized by the abrupt onset of heart failure, bradycardia, lactic acidosis, hyperlipidemia, and rhabdomyolysis (59,60). The underlying mechanism is not clear, but this syndrome is usually associated with prolonged, high-dose propofol infusions (>4-6 mg/kg/hr for longer than 24 to 48 hrs) (59,60). The triad of bradycardia, hyperlipidemia, and rhabdomyolysis are unique features that help to distinguish this syndrome from septic shock. Treatment involves prompt discontinuation of the drug, supportive care, and cardiac pacing when needed. The mortality is high (>80%) despite therapeutic efforts (59). Maintaining propofol infusions below a rate of 4 mg/kg/hr may reduce the risk of this deadly condition (59).

Dexmetomidine

Dexmetomidine was introduced in 1999 as an intravenous sedative that does not produce respiratory depression (61,62).

Actions and Uses

Dexmetomidine is a highly selective alpha2-adrenergic agonist that produces sedation, anxiolysis, mild analgesia, and sympatholysis (61). Following a bolus dose of the drug, sedation is evident in a few minutes, and the effect lasts less than 10 minutes. Because of the short duration of action, dexmetomidine is usually given by continuous infusion.

The absence of respiratory depression makes dexmetomidine an appealing sedative for patients who are prone to drug-induced respiratory depression (e.g., patients with sleep apnea or chronic obstructive lung disease), especially when these patients are weaning from mechanical ventilation (62).

Preparation and Dosage

Dexmetomidine is given as a loading dose of 1 μg/kg (infused over 10 minutes), followed by a continuous infusion of 0.2 to 0.7 μg/kg/hr (see Table 49.6). Mild hypertension in response to the loading dose is observed in 15% of patients (due to a-adrenergic stimulation) (61). This effect is usually transient, but it can be minimized by giving the loading dose over 20 minutes. Drug infusions should not be continued for longer than 24 hours (see later), and the dose should be reduced in patients with severe liver dysfunction (61).

Adverse Effects
Adverse effects during dexmetomidine infusion include hypotension (30%) and bradycardia (8%) (61). The latter effect can be severe in patients older than 65, and in the presence of advanced heart block. There is a risk for agitation and "sympathetic rebound" following drug withdrawal (similar to that observed with clonidine). To minimize this risk, **dexmetomidine infusions should not be continued for longer than 24 hours.**

Haloperidol

Haloperidol (Haldol) is an appealing sedative for ICU patients because there is little or no risk of cardiorespiratory depression. Haloperidol is also effective in calming patients with delirium (i.e., agitation or confusional anxiety). The intravenous route has yet to receive approval by the FDA, but intravenous haloperidol has been described in over 700 publications (63) and is supported by the practice guidelines of the Society of Critical Care Medicine (1).

Actions
Haloperidol produces its sedative and antipsychotic effects by blocking dopamine receptors in the central nervous system. Following an intravenous dose of haloperidol, sedation is evident in 10 to 20 minutes, and the effect lasts for hours. The prolonged duration of action makes haloperidol poorly suited for continuous infusion (63). Sedation is not accompanied by respiratory depression, and hypotension is unusual unless the patient is hypovolemic or receiving a beta-blocker.

USES. Due to its delayed onset of action, haloperidol is not indicated for immediate control of anxiety. A benzodiazepine (e.g., lorazepam 1 mg) can be added to achieve more rapid sedation (64). Haloperidol is often targeted for the patient with delirium. However, because of the lack of respiratory depression, the drug can be used to sedate ventilator-dependent patients, and to facilitate weaning from mechanical ventilation (63).

DOSAGE. The dose recommendations for intravenous haloperidol are shown in Table 49.7. These doses are higher than the usual intramuscular doses, and amounts up to 1200 *mg/day* have been well tolerated (63). Individual patients show a wide variation in serum drug levels after a given dose of haloperidol (64). Therefore, if there is no evidence for a sedative response after 10 minutes, the dose should be doubled. **If** there is a partial response at 10-20 minutes, a second dose can be given along with 1 mg lorazepam (64). Lack of response to a second dose of haloperidol should prompt a switch to another agent.

Adverse Effects
Dopamine antagonism in the basal ganglia can cause extrapyramidal reactions; however, these are uncommon when haloperidol is given intravenously (64). The incidence of extrapyramidal reactions is further decreased when haloperidol is given in combination with a benzodiazepine (64). Halperidol should be avoided in patients with Parkinson's disease.

TABLE 49.7 Intravenous Haloperidol for Sedation

Severity of Anxiety	Dose
Mild	0.5-2 mg
Moderate	5-10 mg
Severe	10-20 mg

1. Administer dose by IV push.
2. Allow 10-20 minutes for response:
   a. If no response, double the drug dose, or
   b. add lorazepam (1 mg)
3. If still no response, switch to another sedative.
4. Give ~ of the loading dose every 6 hours for maintenance of sedation.

Adapted from References 1, 63.

The most feared adverse effects of haloperidol are the neuroleptic malignant syndrome and torsades de pointes (polymorphic ventricular tachycardia). The neuroleptic malignant syndrome (described in detail in Chapter 38) is a rare idiosyncratic reaction that presents with hyperthermia, severe muscle rigidity, and rhabdomyolysis, and has been reported in ICU patients receiving intravenous haloperidol (65). Torsades de pointes is a characteristic form of ventricular tachycardia (see Figure 18.7) that is caused by drugs like haloperidol that prolong the QT interval on the electrocardiogram (56). This reaction is reported in up to 3.5% of patients receiving intravenous haloperidol (66) and, for this reason, haloperidol should be avoided in patients with a prolonged QT interval or a prior history of torsades de pointes.

INTERRUPTION OF DRUG INFUSIONS

Prolonged infusions of sedatives and analgesics are accompanied by progressive drug accumulation and persistent sedation after the drug infusion is discontinued. In recovering patients, daily interruption of drug infusions is associated with a shorter duration of mechanical ventilation, a reduced length of ICU stay, and fewer diagnostic tests to evaluate depressed consciousness (67). When patients have been maintained on sedative and analgesic drug infusions for longer than 24 hours and are beginning to recover, daily interruptions of drug infusions for a time period sufficient to allow patient awakening is recommended (67).

AN APPROACH TO THE AGITATED PATIENT

A common scenario in the ICU is a nurse informing you that your patient has suddenly become agitated. The flow diagram in Fig. 49.3 might help in this situation. When you arrive at the bedside, your first priority is to

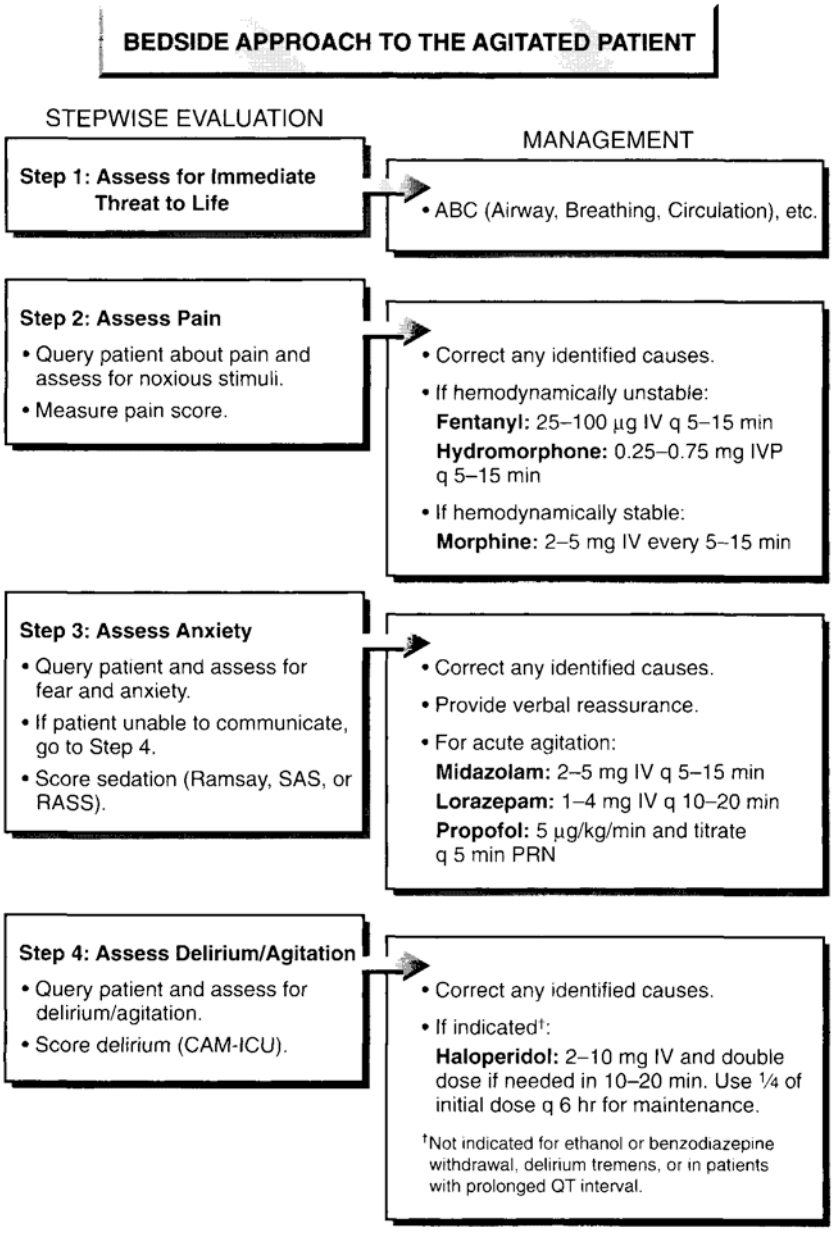

FIGURE 49.3 Bedside approach to the patient with acute agitation. The drug therapy in this figure is intended only for initial patient comfort and should be followed by regular or continuous drug administration to maintain the desired level of comfort. See Appendix for SAS, RASS, and CAM-ICU scoring methods. (Adapted from Jacobi J, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119–141.)

exclude an immediate threat to life (review the patient's ABCs, Airway, Breathing, and Circulation). Then proceed by considering the following conditions in order: pain, anxiety, and delirium. For each condition, ask the patient if the conditlun is present and, if present, assess the severity using an appropriate clinical scoring system. Then attempt to identify and correct the cause, and use the appropriate medication to alleviate symptoms. If the first condition (pain) is not present, proceed to the second condition, and so on.

A FINAL WORD

Patient comfort often gets overlooked in the rapid pace of patient care in the ICU. Remember to ask your patients regularly if they are comfortable and free of pain, especially when they're unable to verbalize discomfort due to an endotracheal tube. Also remember that the therapeutic dose of analgesic and sedative drugs differs for each patient, so use the recommended drug doses as a starting point, and titrate the dose as needed until the patient is comfortable. Finally, when the patient begins to recover, start daily wake-up tests to prevent unwanted prolongation of drug effects. These simple measures may be the most important therapy you have to offer your patients during their stay in the ICU.

REFERENCES

Chapter 50

DISORDERS OF MENTATION

"If one subject ... can *be said* to *be at once well settled and persistently unresolved, it is how* to *determine that death has occurred."*
Alexander Morgan Capron. 200I

Abnormal mental function is one of the most recognizable signs of serious illness. Disordered mentation occurs in over 80% of ventilatordependent patients, and is associated with a 3-fold increase in mortality, as well as a longer stay on the ventilator and in the ICU (1,2). Despite its profound significance, mental dysfunction often goes undetected, as will be described.

This chapter begins by focusing on two disorders of mental function that are common in critically ill patients: altered consciousness and delirium. The final section then describes the most severe disorder of mental function that will ever be encountered: brain death (3-7).

MENTAL FUNCTION

The "mental" aspect of brain function is responsible for the manner in which individuals interact with their environment. Mental function is considered normal when all the following mental processes are intact:

Awareness of self and surroundings.

Ability to accurately perceive what is experienced (sensory input and orientation).

Ability to store and retrieve information (memory).

Ability to process input data to generate more meaningful information (judgment and reasoning).

The first mental process is known as *consciollsness,* while the latter three mental processes make up what is known as *cognition.* The disorders of mental function can therefore be classified as *disorders of consciousness* and *disorders of cognition.*

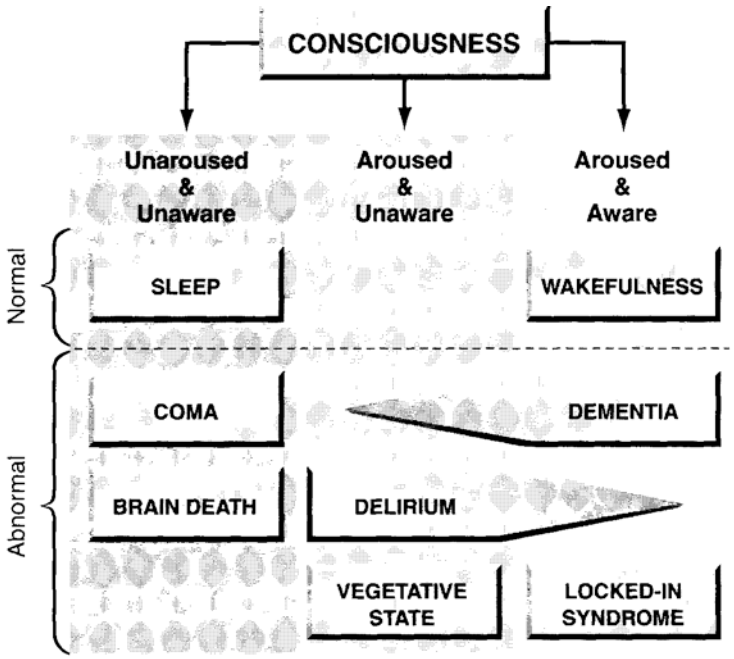

FIGURE 50.1 Diagram depicting states of consciousness.

Disorders of Consciousness

Consciousness has two components: *arousal* (or wakefulness) and *awareness* (or responsiveness). These two components are used to identify the major conditions of normal and abnormal consciousness in Figure 50.1. These conditions are briefly described below.

Normal mentation is characterized by awareness (wakefulness) or arousability (sleep).

Delirium and **dementia** are conditions where arousal is associated with varying degrees of awareness. (The features that distinguish these two conditions are described later in the chapter.)

Vegetative state is characterized by arousal (eyes open) with no awareness (8). Spontaneous movements can occur but are purposeless. After one month, this condition is called a *persistent vegetative state.*

Locked-in state can mimic a vegetative state, but awareness is intact. This disorder is caused by bilateral injury to the motor pathways in the ventral pons disrupting all voluntary movement except for up-down ocular movements and eyelid blinking (9). Function of the cortex and the reticular activating system are unaffected, and the patient is fully awake and aware.

Coma is characterized by the absence of arousal and awareness; i.e., it is a state of *unarousable unawareness.*

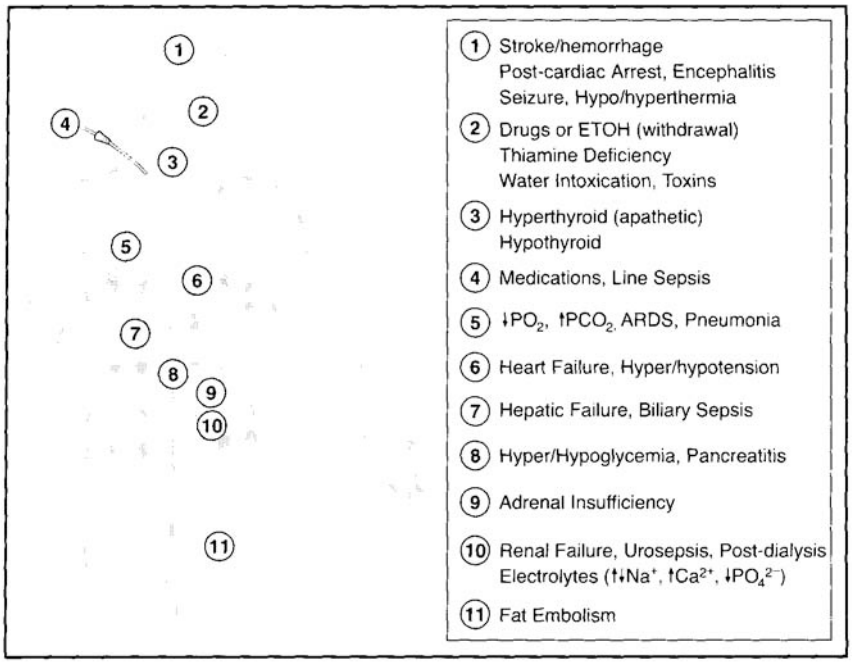

FIGURE 50.2 Possible causes of abnormal mental function.

Brain death is similar to coma in that it is a state of unarousable unawareness. However unlike coma, brain death is irreversible, and is accompanied by cessation of all functions of the brain, including the brainstem **(O)**.

Etiologies of Altered Consciousness

The most common causes of altered consciousness in patients who have not sustained a head injury (nontraumatic) are listed in Figure 50.2. Most of the conditions listed in this figure can be classified as types of *encephalopathies,* which are global brain disorders triggered by factors extrinsic to the central nervous system (e.g., infectious, ischemic, drug-related, or metabolic) (3,11,12). In a prospective survey of neurologic complications in a medical ICU (13), ischemic stroke was the most frequent cause of altered consciousness on admission to the ICU, and septic encephalopathy was the most common cause of altered consciousness that developed *after* admission to the ICU.

Septic Encephalopathy

Septic encephalopathy is the result of infections that originate outside the central nervous system. It is reported in 50-70% of ICU patients with sepsis, and can be an early sign of sepsis, particularly in the elderly (12,13). The encephalopathy can be the result of any of the following processes

(12,14): 1) The blood brain barrier function is abnormal and can result in cerebral edema; 2) Inflammatory mediators can cross the blood brain barrier and impair brain function; 3) The brain concentration of aromatic amino acids and ammonia are increased (similar to hepatic encephalopathy) and brain function can improve when the intake of aromatic amino acids is reduced or eliminated; and 4) eerebral blood flow is *decreased* to about 60% of normal and, when combined with hyperventilation (in response to metabolic acidosis), cerebral ischemia can result (15).
Although the mechanism is unclear, septic encephalopathy appears to be caused by the systemic inflammatory response to sepsis, rather than the infection itself. In fact, septic encephalopathy can be one manifestation of a more widespread multiorgan injury associated with *the systemic inflammatory response syndrome* (see Chapter 40).

Delirium
Delirium is the most common mental disorder in ICUs, and is reported in as many as 87% of mechanically ventilated patients (2,16). **It** is also the most common mental disorder in hospitalized elderly patients, and is the most common postoperative complication in the elderly (3). Patients who develop delirium have a 3-fold greater risk of death (2,3).
Over 40% of hospitalized patients with delirium have psychotic symptoms (with visual hallucinations being most common) (7). This condition has been called "ICU psychosis" but a more accurate term is "delirium with psychotic features" (18). Unfortunately, as many as twothirds of delirium episodes go unnoticed (19).

CLINICAL FEATURES. The clinical features of delirium are summarized in Figure 50.3 (16). Delirium is a cognitive disorder characterized by attention deficits, and either disordered thinking or an altered level of consciousness. The hallmark of delirium (and the feature that distinguishes it from dementia) is its acute onset or fluctuating clinical course.

Hypoactive Delirium
There is a tendency to consider delirium as a state of agitation (as in the delirium tremens syndrome). However, as shown in Figure 50.3, there is also a hypoactive form of delirium that is characterized by lethargy rather than agitation. In fact, hypoactive delirium is the most common form of delirium in the elderly (2). This is certainly a source of missed diagnoses of delirium in many patients.

Delirium vs. Dementia
Delirium and dementia are distinct mental disorders that are easily confused because of overlapping clinical features (e.g., attention deficits and abnormal thinking) (20). As noted above, the principal features of delirium not present in dementia are its acute onset and/or fluctuating course. As many as two-thirds of hospitalized patients with dementia can have a superimposed delirium (3,20), and the delirium can provoke further mental and functional decline (3).

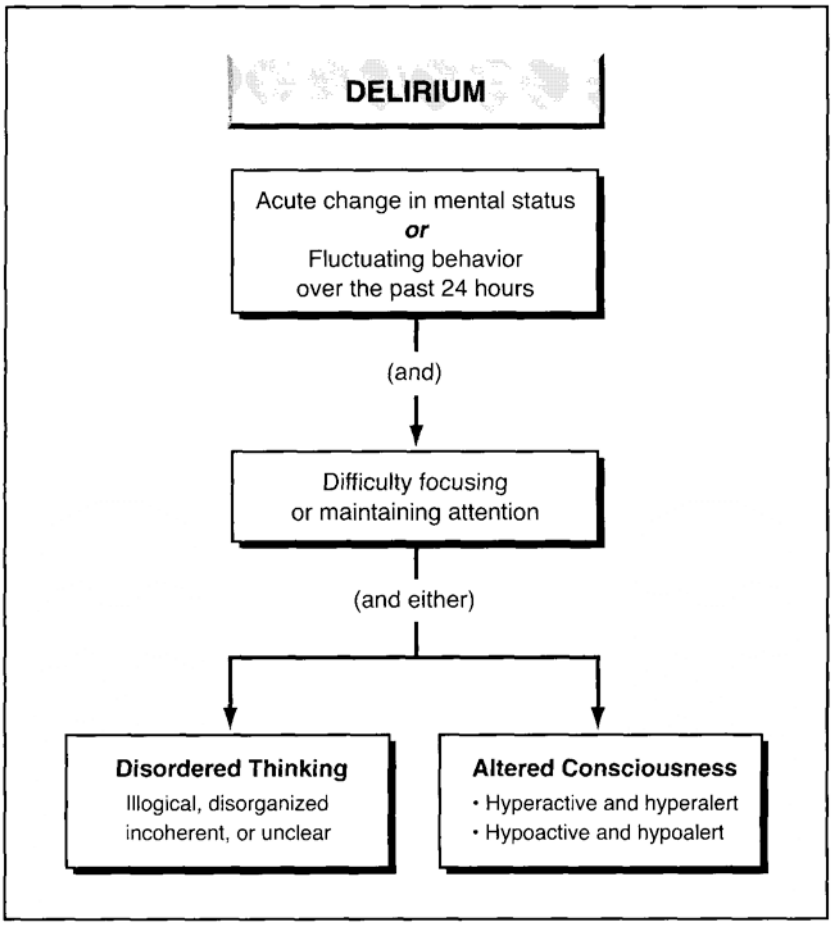

FIGURE 50.3 The clinical features of delirium.

Etiologies

The possible causes of delirium are listed in Figure 50.2. Any type of encephalopathy (i.e., infectious, ischemic, drug-related, or metabolic) can cause a state of delirium. Drugs are implicated as causative or contributory factors in as many as 40% of cases of delirium in the elderly (11). The drugs most likely to be responsible for delirium in ICU patients are listed in Table 50.1 (3,11,18). The principal offenders in this list are alcohol (withdrawal), the long-acting benzodiazepines (lorazepam and diazepam), and opioids.

Management

The management of delirium should focus on identifying and treating the underlying cause of the problem. In addition, the following measures

TABLE 50.1 Medications That Can Cause Delirium in the ICU·

Alcohol (withdrawal)	Corticosteroids (high-dose)
Amphotericin	Digitalis
Aminoglycosides	H_2-Blockers (e.g., cimetidine, ranitidine)
Angiotensin-converting enzyme inhibitors	Isoniazid
Anticholinergics (atropine)	Local anesthetics (lidocaine, bupivacaine)
Anticonvulsants (e.g., phenytoin)	Metoclopramide
Antidysrhythmics (e.g., quinidine, amiodarone)	Metronidazole
Benzodiazepines (e.g., lorazepam)	NSAIDs (e.g., ibuprofen)
l3-Blockers	Opioids (especially meperidine)
Cephalosporins	Penicillin (high-dose)
Cocaine	Trimethoprim-su Ifamethoxazole

'List is limited to drugs that are likely to be encountered in ICU patients.

may be helpful: provide reassurance and reorientation, assess for and treat pain, maintain normal sleep cycles and avoid sleep interruption, encourage family visitation, place patient in an ICU bed with a window, avoid physical restraints and urinary bladder catheters, and provide patient with eyeglasses and hearing aid (3,11).

Pharmacologic Management

If agitation and disruptive behavior become a problem, the administration of sedatives may be beneficial. The choice of sedative is determined by the cause of the delirium, as described below (3,11,21,22).

For ICU-acquired or postoperative delirium, the treatment of choice is haloperidol (0.5 to 2 mg PO or IV every 4-6 hours as needed) (3,11). Benzodiazepines should be avoided in these cases because they can aggravate the delirium (3).

For delirium that accompanies alcohol withdrawal, benzodiazepines are preferred (see Table 49.4 for benzodiazepine dosing recommendations) (21). Haloperidol should be avoided in these cases because it can aggravate the delirium, and it does not prevent seizures (21).

If delirium tremens is accompanied by troublesome hypertension, adjunctive therapy with clonidine (a centrally-acting alpha-2 agonist) can augment the sedative effect of benzodiazepines while it decreases the blood pressure. elonidine does not prevent delirium or seizures, and should always be used in combination with a benzodiazepine (21). The dose of clonidine is 0.1 mg orally every 2-4 hours until the pressure is controlled or a cumulative dose of 0.5 mg has been given.

The management of cocaine-induced delirium is the same as delirium tremens; i.e., benzodiazepines are preferred, while haloperidol is not advised (22).

COMA

Because of the vast reserves of the brain, persistent unarousability (lasting more than 6 hours) implies extensive brain injury (23). The most common causes of coma in one study were cardiac arrest (31 %), and either stroke or intracerebral hemorrhage (36%) (23). The anatomic basis of coma and associated findings are summarized below (7,24):

Diffuse and bilateral cerebral damage (brainstem reflexes may remain intact).

Unilateral cerebral damage causing midline shift with compression of the contralateral cerebral hemisphere.

Supratentorial mass lesion causing transtentorial herniation and brains tern compression (producing ipsilateral third nerve palsy with a fixed dilated pupil and contralateral hemiplegia).

Posterior fossa mass lesion causing direct brainstem compression (often associated with the *Cushing reflex* of bradycardia and hypertension).

Toxic or metabolic disorders (small or mid position, light-reactive pupils).

Coma is rarely a permanent state, but less than 10% of patients survive coma without significant disability (23). For ICU patients with persistent coma, the outcome is grim. In one study of ICU patients, all patients who failed to awaken from coma died after a median duration of 3 days (2).

Bedside Evaluation of Coma

The bedside evaluation of coma must include an assessment of brainstem reflexes, and the following information deserves mention.

Pupils

The conditions that affect pupillary size and light reactivity are shown in Table 50.2 (4,24-26). In the presence of coma, pupillary function may be normal if the brain lesion is above (rostral to) the midbrain (4), or if the patient is receiving neuromuscular blockers (without sedatives) (27).
If the injury is diffuse (e.g., global cerebral anoxia-ischemia), the pupillary abnormality is bilateral. When a brain insult causes cerebral anoxic-ischemia (e.g., cardiac arrest), the pupils become bilaterally dilated and nonreactive, and rapid resuscitation can restore (or even maintain) normal pupil size and light response. When atropine is given in the usual doses during CPR, the pupils will dilate

TABLE 50.2 Conditions That Affect Pupillary Size & Reactivity

Pupillary Size	Reactive	Nonreactive	
Dilated	Atropine (low dose)	Uncal herniation,	Drugs (high dose):
	Sympathomimetics	(unilateral pupil)	Atropine
		Post-CPR	Dopamine
		Brainstem injury	Phenylephrine
		Ocular trauma	Amphetamine
		Hypothermia(<28°C)	TCA
Midposition	Toxic/metabolic encephalopathy	Brain death	
	Sedative overdose	Midbrain lesions	
		Barbiturates (high-dose)	
Constricted	Toxic/metabolic encephalopathy	Opioids (high-dose)	
	Pontine injury	Pilocarpine eye drops	
	Opioids		

Abbreviation: TCA: tricyclic

but they usually remain reactive to light (25). **If the pupils remain nonreactive for longer than 6-8 hours after resuscitation from cardiac arrest, the prognosis for neurological recovery is generally poor** (28,29).

A unilateral dilated pupil that is unreactive to light, when combined with contralateral hemiplegia, is highly suggestive of unilateral herniation with compression of the third cranial nerve and midbrain (4). This finding should prompt an immediate search for a potentially correctable abnormality (e.g., hemorrhage) because a unilateral herniation can progress rapidly to irreversible injury.

Ocular Motility

Spontaneous eye movements (conjugate or dysconjugate) are a nonspecific sign in comatose patients and can suggest toxic or metabolic etiologies (24). However, a fixed gaze preference involving one or both eyes is highly suggestive of a mass lesion or seizures.

Ocular Reflexes

The ocular reflexes are used to evaluate the functional integrity of the lower brainstem (24). These reflexes are illustrated in Figure 50.4.

The oculocephalic reflex is assessed by briskly rotating the head from side-to-side. When the cerebral hemispheres are impaired but the lower brainstem is intact, the eyes will deviate away from the direction of rotation and maintain a forward field of view. When the lower brainstem

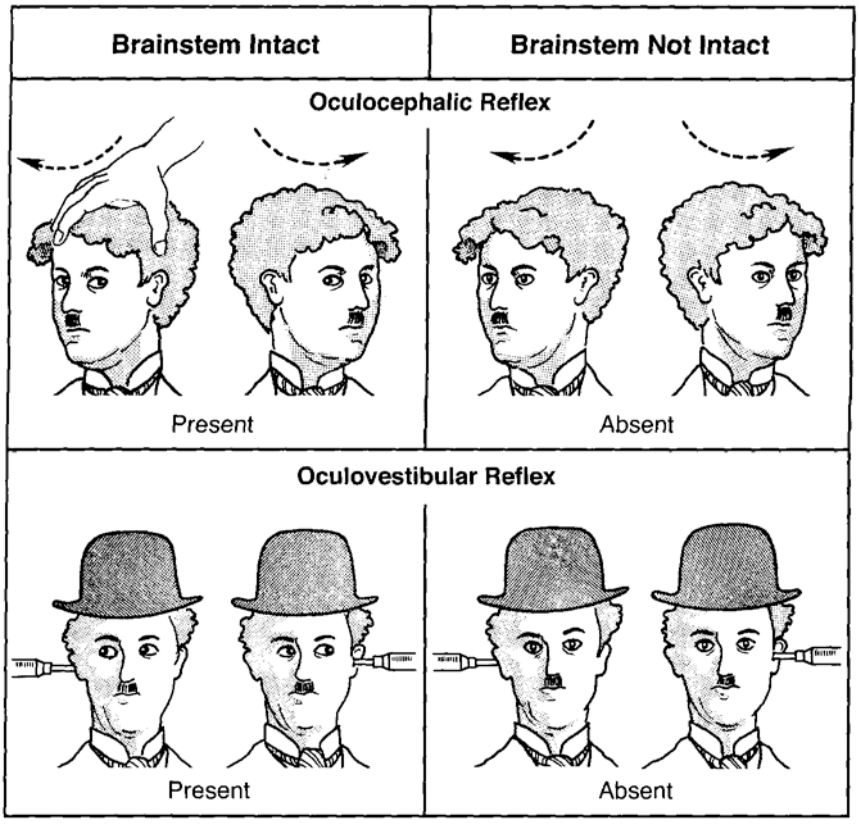

FIGURE 50.4 The ocular reflexes in the evaluation of coma.

is damaged or the patient is awake, the eyes will follow the direction of head rotation. The oculocephalic reflex should *not* be attempted in patients with an unstable cervical spine.

The **oculovestibular reflex** is performed by injecting 50 ml of cold saline in the external auditory canal of each ear (using a 50 ml syringe and a 2-inch soft plastic angiocatheter) **(O)**. Before the test is performed, check to make sure that the tympanic membrane is intact and that nothing is obstructing the ear canal. When brainstem function is intact, both eyes will deviate slowly towards the irrigated ear. This conjugate eye movement is lost when the lower brains tern is damaged. After the test is performed on one side, wait 5 minutes before testing the opposite side.

The Extremities

Clonic involuntary movements elicited by flexion of the hands or feet (asterixis) is a sign of a diffuse metabolic encephalopathy (30). A focal motor or sensory defect in the extremities (e.g., hemiparesis or asymmetric reflexes) is occasionally caused by a diffuse metabolic encephalopathy.

However, the presence of focal neurologic defects should always prompt further investigation (with computed tomography) for a structural brain lesion. In general, motor responses are characterized as appropriate, posturing, or flaccid. With mild mental clouding, there is no response to verbal command, but painful stimulation elicits a purposeful response to remove the stimulus (localizes to pain). With progressive impairment, there is withdrawal of the extremity that is subjected to painful stimulus. With injury to the thalamus, painful stimuli provoke flexion of the upper extremity; this is called *abnormal flexion* or *decorticate posturing.* With injury to the midbrain and upper pons, the arms and legs extend and pronate in response to pain; this is called *abnormal extension* or *decerebrate posturing.* Finally, with injury that involves the lower brainstem (medulla), the extremities become flaccid.

The Glasgow Coma Scale

The severity of altered consciousness is often evaluated with the Glasgow Coma Scale, which is shown in Table 50.3. The scale consists of three

TABLE 50.3 The Glasgow Coma Scale and Score

Eye Opening:	Points	
Spontaneous	4	
To speech	3	
To pain	2	
None	1	Points
Verbal Communication:		
Oriented	5	
Confused conversation	4	
Inappropriate but recognizable words	3	
Incomprehensible sounds	2	
None	1	Points
Motor Response:		
Obeys commands	6	
Localizes to pain	5	
Withdraws to pain	4	
Abnormal flexion (decorticate response)	3	
Abnormal extension (decerebrate response)	2	
No movement	1	Points
Glasgow Coma Score (Total of 3 scales)*		Points

'Worst score is 3 points, and best score is 15 points. With endotracheal highest score is 11.

components: 1) eye opening, 2) verbal communication, and 3) motor response to verbal or noxious stimulation (31,32). The Glasgow Coma Score is the sum of the three components, and has a range from 3 to 15 (31,32).
The Glasgow Coma Score can be used as follows (28,32,34).

To define coma (GCS <=8).

To stratify the severity of head injury (mild 13-15, moderate 9-12, severe <=8)

To identify candidates for intubation (i.e., patients with GCS <=8 are usually unable to protect their airway and require endotracheal intubation).

As a prognostic marker; e.g., in the initial evaluation of nontraumatic coma, patients with a GCS >=6 are seven-times more likely to awaken within two weeks than patients with a GCS <=5 (33).

The verbal communication component of the GCS is a problem in ICU patients who are intubated, since these patients are unable to communicate verbally (34).

Predictive Value
The predictive values of the components of the Glascow eo rna Scale are shown in Table 50.4. In this case, the predictive value refers to the chances of a satisfactory neurological recovery in patients who remain comatose after resuscitation from cardiac arrest (28). In patients who show no response to verbal or noxious stimuli at one hour after the cardiac arrest, 70 to 80% will not have a satisfactory neurological recovery. At 24 hours following cardiac arrest, absent pupillary light and corneal reflexes greatly increases the likelihood of an unfavorable outcome (35). If the

TABLE 50.4 Predictive Value of the Pupillary Light Response and the Glasgow Coma Scale Following Cardiac Arrest

	Negative Predictive Value Post-Arrest		
	1st hour	24 hours	3 days
Parameter	(%)	(%)	(%)
Absent pupillary response to light·	83	93	100
No eye opening to pain	69	92	100
No response to verbal stimuli	67	75	94
No motor response to pain	75	91	100
Glasgow Coma Score less than 6	69	–	100

Data from Edgren E, Hedstrand U, Kelsey S, et al. Assessment of neurological in comatose survivors of cardiac arrest. Lancet 1994;343:1055-1059.

TABLE 50.5 The Clinical Criteria of Brain Death in Adults

Instructions: When Steps 1, 2, and 3 are confirmed, the patient is declared brain dead.	**Check (✓) Item if Confirmed**	
Step 1: Prerequisite to Exam		
Evaluate and correct potentially reversible causes of the abnormal neurological examination. 1. Hypotension (mean arterial pressure <60 mm Hg, arbitrary) 2. Hypothermia (core temperature <32°C or <90°F) 3. Metabolic disturbances (i.e., glucose, electrolyte, acid-base, or endocrine) 4. Significant drugs or medications 5. Confounding diseases (e.g., locked-in syndrome, Guillain-Barré)	☐	
The cause of coma is known and sufficient to account for irreversible brain and brainstem death. Clinical history and/or neurological imaging are consistent with brain death.	☐	
Step 2: Absence of Brain and Brainstem Function This step involves two exams, usually performed 6 hours apart.	**First Exam**	**Second Exam**
Coma: Absent cerebral motor response in all extremities *and* face to noxious stimuli (nail-bed and supraorbital ridge pressure).	☐	☐
Absent Brainstem Reflexes:		
Pupils		
• Size: midposition to dilated (4 to 9 mm)	☐	☐
• Absent response to bright light	☐	☐
Absent corneal reflex (touch edge of cornea)	☐	☐
Absent gag reflex (stimulate pharynx)	☐	☐
Absent cough response (tracheobronchial suction)	☐	☐
Ocular Movement		
• Absent oculocephalic reflex (perform only if cervical spine is stable)	☐	☐
• Absent deviation of eyes with cold water stimulation of the tympanic membranes	☐	☐
Step 2a: Consider Confirmatory Test* if Steps 1 or 2 cannot be fully performed or adequately interpreted.		
Step 3: Absence of Respiratory Effort†		
Positive Apnea Test: Absent respiratory efforts when the arterial PCO_2 increases by more than 20 mm Hg above the patient's normal baseline.	☐	
Step 3a: Consider Confirmatory Test* if Step 3 cannot be fully performed or adequately interpreted.		

***Confirmatory Testing**

These conditions may warrant confirmatory tests: 1) significant levels of drugs (e.g., sedatives, neuromuscular blocking agents, anticholinergics, organophosphates, tricyclic

(*Continued*)

(*Continued)*
antidepressants, antiepileptic drugs), 2) severe facial trauma, 3) cervical spinal cord injury, 4) preexisting pupillary abnormalities, or 5) severe pulmonary disease and chronic hypercapnia. Confirmatory test options include: cerebral angiography, brain scan with technetium-99m, electroencephalography, transcranial doppler, or somatosensory evoked potentials. (See references for details.)
tApnea Test
Prerequisites: 1) Begin test at patient's normal baseline arterial $PC0_2$ (never less than 40 mm Hg), 2) T ""36SC (9rF), systolic BP ""90 mm Hg.
Perform test: 1) Preoxygenate with 100% 02' 2) monitor BP and pulse oximetry, 3) deliver 100% 02 via canula into the trachea to maintain oxygenation, 4) observe for respiratory movements, 5) measure arterial P02' $PC0_2$, and pH after at least 8 minutes and reconnect the ventilator.
Abort test: Draw blood gas and reconnect ventilator for: 1) spontaneous respirations or movement, 2) systolic BP :590 mm Hg, 3) oxygen desaturation, or 4) cardiac dysrhythmias.
Modified from: 1) Practice Parameters for Determining Brain Death in Adults. Neurology, 1995.45:1012-1014, and 2) Wijdicks EF. The diagnosis of brain death. N Engl J Med 2001 :344:1215-1221.

neurological deficits persist after 3 days following the cardiac arrest, the chances for recovery are practically nil (28).
The data in Table 50-4 also demonstrate that the Clascow eoma Scale does not reach its full predictive power in the first few hours after cardiac arrest. Therefore, the Glascow Coma Scale should not be used to predict the chances for neurological recovery in the first few hours after cardiac arrest.

BRAIN DEATH
As mentioned earlier, brain death is a condition of irreversible cessation of function in the entire brain, including the brainstem. This condition is most often the result of cardiac arrest, intracerebral hemorrhage or infarction, or trauma. Regardless of the primary event, brain death usually results from widespread brain edema, elevation of intracranial pressure, and irreversible cessation of blood flow to the brain and brainstem (36). Brain death is not a common consequence of the conditions listed in Figure 50.2

Diagnosis
The lack of consensus regarding the diagnosis of brain death makes it impossible to state one unifying set of diagnostic criteria (37). In fact, distinct differences in diagnostic criteria vary by country and even state, and mandate consulting local guidelines. A checklist for the diagnosis of brain death in adults is shown in Table 50.5.
Prior to performing a brain death examination, other confounding conditions (e.g., locked-in syndrome, hypothermia) should be excluded

. The goal of the brain death determination is to establish: 1) irreversible coma, 2) the absence of brain stem reflexes, and 3) the absence of spontaneous respirations. If the etiology of the coma is unknown, or if part of the clinical examination cannot be performed (e.g., ocular injury), then confirmatory testing (e.g., cerebral blood flow studies) can help make a definitive diagnosis.

Apnea Testing

The hallmark of the brain death examination is the demonstration of the persistent absence of all respiratory efforts in the presence of an acute increase in arterial pCO2. Because the apnea test can cause hypotension, hypoxemia, and cardiac dysrhythmias, it best to make this the last step in brain death determination. Prior to the test, the patient is preoxygenated with 100% 0z and minute ventilation is set to the patient's normal baseline arterial peo_z (but never less than 40 mm Hg). Next, the patient is separated from the ventilator, oxygen is insufflated into the endotracheal tube (apneic oxygenation helps prevent desaturation), and the peo_z rises at about 3 mm Hg per minute. Because hypothermia slows metabolism and the rate of rise of CO2 in the blood (38), the apnea test should be performed only after normothermia has been established. After 8-10 minutes of apnea, the arterial blood is sampled and the patient should be briefly hyperventilated and then placed back on mechanical ventilation at the pre-test ventilator settings. If apnea persists despite a rise in the arterial $pCO2_z$ > 20 mm Hg, the test is positive and consistent with a diagnosis of brain death. If there are complications, hypotension, desaturation, or significant cardiac dysrhythmias, the apnea test is aborted and an arterial blood sample is drawn to determine whether the increase in arterial pCO2 is adequate to satisfy conditions of the test.

In the absence of normal sympathetic tone, hypercapnia causes a decline in left ventricular function and peripheral vasodilation. Thus, it is not surprising that hypotension is the most commonly observed hemodynamic alteration during an apnea test, with an incidence of 24% (39).

Brain dead patients can exhibit brief, spontaneous movements of the head, torso, or upper extremities *(Lazarus' Sign),* especially after they are removed from the ventilator. These movements are likely due to cervical spinal cord neuronal discharges in response to hypoxemia or mechanical stimulation (40). After the movements cease, the extremities become flaccid.

The Potential Organ Donor

For the potential organ donor, the following measures can be used to enhance organ viability (41).

Hemodynamics

Hypotension (MAP <=60 mm Hg), reduced urinary output <1 mL/kg per hour), or reduced cardiac output <2.4 L/min/m_2) should be corrected with fluid resuscitation (to a CVP 6-8 mm Hg or a PCWP 8-12 mm Hg) followed by either dopamine (for hypotension) or dobutamine (for reduced

cardiac output) if necessary. The dose of vasopressors should be minimized to help maintain organ perfusion. Pulmonary artery catheterization can be helpful because there may be poor correlation between left and right heart filling pressures (42).

Pituitary Failure

More than half of patients with brain death will develop pituitary failure with diabetes insipidus and secondary adrenal insufficiency (43). Both conditions can lead to profound hypovolemia (and reduced organ perfusion) and hypertonic hypernatremia (and cell dehydration). If there is evidence of central diabetes insipidus (Le., spontaneous diuresis with a urine osmolality below 200 mOsm/L), treatment with desmopressin, a vasopressin analog that does not cause vasoconstriction, is advised (44). The usual dose of desmopressin is 0.5 to 2.0 μg IV every 2-3 hours and the dose is titrated to maintain a urine output of about *100-200* ml/hr. Hyperglycemia is also common, especially when dilute dextrose solutions are used to treat hypovolemic hypematremia, and insulin replacement is required to maintain serum glucose between 80 and 150 mg/dL (41). Surprisingly, multiple pituitary failure is uncommon in the first few days after brain death, and levels of TSH and AeTH are normal or elevated (45,46). When blood pressure and cardiac function remained depressed despite hemodynamic optimization, hormone replacement therapy (e.g., methylprednisolone and triiodothyronine) can improve organ function and recovery (47,48).

A FINAL WORD

The care of the comatose patient involves as much (if not more) time with families and loved ones, and nothing is more frightening to them than the possible loss of life or independent function on the part of the patient. Be compassionate, but above all, be honest. Avoiding the *conspiracy of silence* (49) is one of the greatest services you can perform as a physician.

References

Chapter 51

DISORDERS OF MOVEMENT

This chapter focuses on three general types of movement disorders encountered in critically ill patients: (1) involuntary movements (seizures), (2) weak or ineffective movements (neuromuscular weakness), and (3) no movements (neuromuscular blockers).

SEIZURES

Seizures are second only to metabolic encephalopathy as the most common neurological complication following admission to the ICU 0). The incidence of new-onset seizures in ICU patients is 0.8% to 3.5% 0,2).

Definitions

The following definitions will prove helpful in the description, evaluation, and treatment of seizures (3-5).

Types of Movement

Seizures can be accompanied by any of the following patterns of muscular activity: *tonic* contractions (sustained muscle contraction), *atonic* contractions (absence of postural muscle contraction), *clonic* contractions (periodic symmetric body and extremity movements with regular amplitude and frequency), or *myoclonic* contractions (abrupt shock-like muscle contractions with an irregular amplitude and frequency) (5). Seizures can be accompanied by familiar movements known as a*utomatisms* (e.g., lip smacking or chewing). The *post-ictal* period refers to the time immediately following a seizure and there may be transient impairment of mentation and sensorium.

Generalized Seizures

Generalized seizures arise from symmetric and synchronous electrical discharges involving the entire cerebral cortex. These seizures mayor

may not be accompanied by muscle contractions. *Atonic seizures* cause a brief loss of motor tone (drop attack) that can cause falling. *Absence seizures* (formerly known as petit-mal seizures) are brief (usually <10 seconds) and are associated with less prominent changes in muscle tone (e.g., tonic, clonic, atonic, or automatisms). *Generalized tonic-clonic seizures* have an initial tonic phase, which is associated with apnea and cyanosis, followed by a clonic phase where respirations become labored (5).

Partial Seizures

Partial seizures originate as abnormal electrical discharges that are confined to a focal or restricted part of the cerebral cortex. They are subdivided into *simple partial seizures* (do not impair consciousness), *complex partial seizures* (cause impaired consciousness) and *partial seizures with secondary generalization* (a partial seizure that evolves into a generalized convulsive seizure). Two types of complex partial seizures that deserve mention are *temporal lobe seizures* (characterized by a motionless stare and automatisrns) and *epilepsia partialis continua* (characterized by persistent tonic-clonic movements of the facial and limb muscl~s on one side of the body).

Status Epilepticus

Status epilepticus is defined as more than 30 minutes of continuous seizure activity, or recurrent seizure activity without an intervening period of consciousness (6). The most common and potentially dangerous forms of status epilepticus are described below.

Generalized convulsive status epilepticus is the most common form of status epilepticus. Despite treatment, the mortalityassociated with this type of status epilepticus is 20%-27% (7,8). After about 30 minutes, generalized convulsive status epilepticus can degenerate to non-convulsive status (6).

Non-convulsive generalized status epilepticus (subtle status epilepticus) is associated with minimal or no motor activity and requires electroencephalography for diagnosis. As many as 25% of cases of status epilepticus are nonconvulsive (6), and this condition is responsible for 8% of cases of unexplained coma (9). In fact, the most common seizure recorded during electroencephalographic monitoring of patients with altered mental status is non-convulsive (O). Non-convulsive seizures are often re(ractory to therapy, and are associated with a 65% mortality (8).

Refractory status epilepticus is a seizure that lasts more than 1 or 2 hours or is refractory to therapy with 2 or 3 anticonvulsant agents (11). Almost one-third of cases of status epilepticus are refractory (11).

Myoclonic status epilepticus can occur in up to one-third of patients with persistent coma following out-of-hospital cardiac arrest. This condition is characterized by sound-induced or spontaneous irregular and repetitive movements of the face and extremities (12). When it persists for 24 hours following resuscitation, myoclonic status is a sign of devastating neurological damage (13).

Etiologies

New-onset seizures can be the result of a drug intoxication (e.g., theophylline), drug withdrawal (e.g., ethanol), infections (e.g., meningoencephalitis, abscess), head trauma, ischemic injury (e.g., focal or diffuse), space-occupying lesions (e.g., tumor of hemorrhage), or systemic metabolic derangements (e.g., hepatic or uremic encephalopathy, sepsis, hypoglycemia, hyponatremia, or hypocalcemia) (4). In one survey of new-onset seizures in ICU patients, the most common causes were sedative or opioid withdrawal (33%), severe metabolic abnormalities (33%), and drug intoxication 05%) (2). The drugs most likely to cause seizures in ICU patients are listed in Table 51.1 (3,4).

Status Epilepticus

In one survey, only 10% of patients who develop seizures in a medical ICU go on to develop status epilepticus 0). The most common causes of status epilepticus are noncompliance with or withdrawal of antiepileptic drug therapy, cerebrovascular disease, and alcohol withdrawal (4).

Evaluation

The evaluation of new-onset seizures should focus on the etiologies previously mentioned. In the absence of an obvious and potentially reversible metabolic or drug-related cause, or when the physical exam reveals a focal abnormality, further evaluation (neuroimaging studies and lumbar puncture) is advised. In ICU patients with depressed mental status or

TABLE 51.1 Drug-Related Seizures in the ICU

Drug Intoxication	Drug Withdrawal
Pharmaceuticals:	Barbiturates
Ciprofloxacin	Benzodiazepines
Imipenem	Ethanol
Isoniazid	Opiates
Lidocaine	
Meperidine	
Penicillins	
Theophylline	
Tricyclics	
Drugs of Abuse:	
Amphetamines	
Cocaine	
Phencyclidine	

Adapted from Oelanty N, Vaughan CJ, French JA. Medical causes of
1998;352:383-390.

following an episode of status epilepticus, electroencephalography is necessary to detect non-convulsive seizures, which are the most common type of seizures observed when EEG monitoring is used (O).

Complications
The adverse effects of generalized seizures include hypertension, lactic acidosis, hyperthermia, respiratory compromise, pulmonary aspiration or edema, rhabdomyolysis, self-injury, and irreversible neurological damage (when seizures persist for longer than 30 minutes) (6).

Management
If the seizure stops and the immediate cause is corrected, anti-epileptic medication may not be necessary. Seizures that persist for longer than 5-10 minutes should be treated urgently because of the risk for permanent neurological injury, and also because seizures become refractory to therapy the longer they persist (5). The acute drug management of convulsive seizures is summarized in Figure 51.1 (7,8,15-17). Most neurologists concur regarding the drug management indicated in Steps 1 and 2, and opinions vary regarding agents to be used in Step 3.

Benzodiazepines
Intravenous benzodiazepines will terminate 65-80% of convulsive seizures within 2 to 3 minutes (8,15). Lorazepam (Ativan) in a dose of 0.1 mg/kg IV or diazepam (Valium) in a dose of 0.15 mg/kg IV is equally effective in aborting a generalized seizure (7,15). However, the anticonvulsant effects of lorazepam lasts longer than those of diazepam 02-24 hours vs. 15-30 minutes, respectively), so recurrent seizures are less likely following lorazepam (7,15). Because of its prolonged effect, lorazepam is the initial agent of choice for treatment of convulsive seizures. If diazepam is used, it should be followed immediately by phenytoin to prevent seizure recurrence.

Phenytoins
Intravenous phenytoin has been widely used to treat seizures since 1956. The standard intravenous dose is 20 mg/kg in adults; a smaller dose of 15 mg/kg is recommended in the elderly (6). A maximum infusion rate of 50 mg/min is advised to reduce the risk for cardiovascular depression (which is due to the drug itself and the propylene glycol diluent used in intravenous preparations) (5). If the initial dose of phenytoin is unsuccessful, additional doses can be given to a total cumulative dose of 30 mg/kg (5). The therapeutic serum level for phenytoin is 10 to 20 μg/mL. Phenytoin should not be given in dextrose-containing solutions because it can precipitate (8), and tissue extravasation must be avoided because the highly alkaline pH of 12 can cause tissue necrosis.
Fosphenytoin (Cerebyx) is a prodrug that may be preferred to phenytoin because: 1) it can be infused faster than phenytoin, 2) it does not

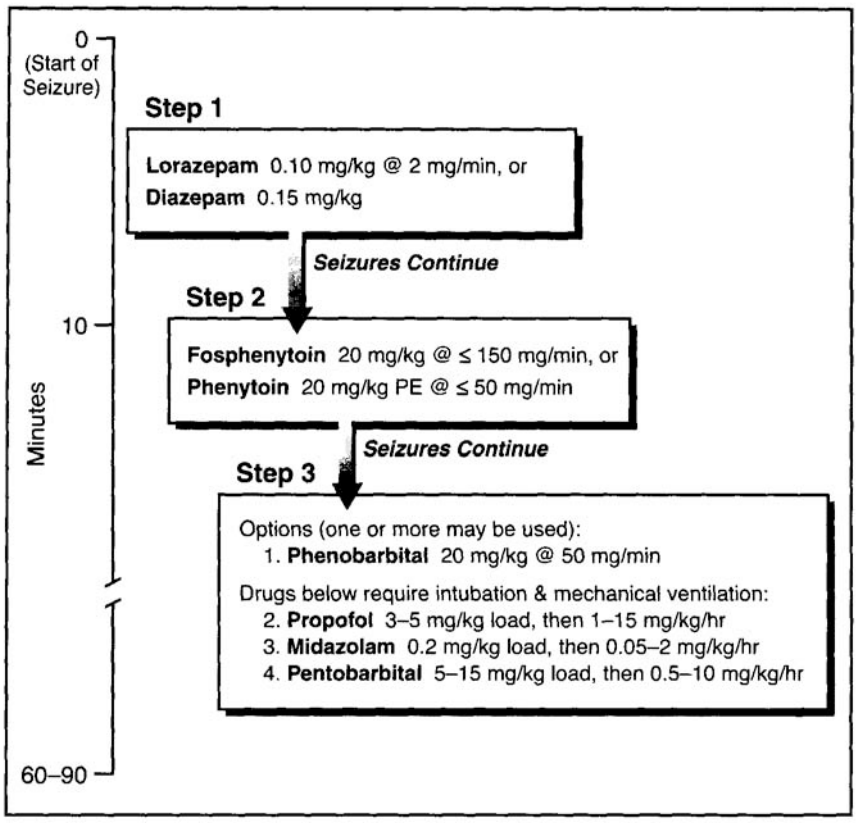

FIGURE 51.1 Intravenous drug therapy for convulsive seizures in the ICU. PE = phenytoin equivalents.

contain propylene glycol (which contributes to cardiovascular depression), 3) it is compatible with dextrose-containing solutions, and 4) drug extravasation does not cause skin necrosis (8). Fosphenytoin is rapidly converted to phenytoin (half life is 7-15 minutes), and the therapeutic doses are the same as those recommended for phenytoin (8). However, the maximum allowable infusion rate for fosphenytoin is 150 mg/min, which is three times faster than phenytoin, so fosphenytoin could produce more rapid suppression of seizures than phenytoin.

Phenobarbital

The combination of benzodiazepines and phenytoin will control seizures in 60-90% of cases of convulsive status epilepticus (11). In refractory cases, intravenous phenobarbital can be effective when given in a dose of 50-75 mg/min until seizures are controlled or a maximum of 20 mg/ kg is achieved. The therapeutic serum level for phenobarbital is 20 to 40 μg/mL. Common side effects include hypotension (usually responsive to IV fluids), respiratory depression, and prolonged sedation (at the

higher dose range). Phenobarbital is also the most effective agent available for the initial treatment of nonconvulsive seizures (8).
Anticonvulsant hypersensitivity syndrome is an uncommon (incidence 1:1,000 to 1:10,000) idiosyncratic reaction to phenytoin or phenobarbital (cross-reactivity is 50%) associated with the triad of fever, rash, and lymphadenopathy (9). Elevated liver enzymes and lymphocytosis occur in up to two-thirds of cases. Treatment involves immediate withdrawal of the offending agent and seizure control with diazepam at 0.05-0.4 mg/kg/hr (20).

Refractory Status Epilepticus
Status epilepticus that is refractory to first and second line agents can be treated with infusions of propofol, midazolam, or pentobarbital (see Figure 51.1), Pentobarbital is the most effective of these agents but it often causes hypotension (21). Refractory cases require endotracheal intubation, mechanical ventilation, and electroencephalographic monitoring. A single dose of neuromuscular blocker may be required to facilitate intubation, but these agents can mask seizures, and EEG monitoring is recommended for continued neuromuscular blockade.

NEUROMUSCULAR WEAKNESS SYNDROMES
The following is a brief description of neuromuscular disorders that can produce severe and life-threatening neuromuscular weakness. Some comparative features of these disorders are included in Tables 51.2 and 51.3 (22-24).

Myasthenia Gravis
Myasthenia gravis is an autoimmune disease that is characterized by antibody-mediated destruction of acetylcholine receptors located at the postsynaptic side of neuromuscular junctions. This condition is uncommon, and affects about 1 in every 100,000 adults (25).

TABLE 51.2 Comparative Features of Myasthenia Gravis and Guillain-Barre Syndrome

Features	Myasthenia Gravis	Guillain-Barre Syndrome
Ocular findings	Yes	No
Fluctuating weakness	Yes	No
Bulbar weakness	Yes	Yes
Deep tendon reflexes	Intact	Depressed
Autonomic instability	No	Yes
Nerve conduction	Normal	Slowed

TABLE 51.3 Comparative Features of Conditions Associated with ICU-Acquired Neuromuscular Weakness

	Critical Illness Polyneuropathy	Residual Neuromuscular Block	Critical Illness Myopathy
Sensory	Moderate to severe	Normal	Normal
Motor	Symmetric weakness, respiratory failure	Symmetric weakness, respiratory failure	Symmetric weakness, respiratory failure
Creatine Kinase	Normal	Normal	Mild elevation in 50%
Electrodlagnostic Studies	Motor & sensory axonal degeneration, normal conduction velocity	Fatigue at neuromuscular junction	Myopathic changes, normal conduction velocity
Muscle Biopsy	Denervation atrophy	Normal	Muscle atrophy, loss of thick (myosin) filaments

Clinical Features

The weakness in myasthenia gravis worsens with repeated activity and improves with rest (25). Signs of weakness are usually first evident in the eyelids and extraocular muscles, and generalized weakness of the limbs follows in 85% of cases (26). The proximal limb muscles are often affected, and weakness can involve the diaphragm and thoracic musculature. Weakness of pharyngeal muscles can impair swallowing and predispose to pulmonary aspiration. Rapid progression to respiratory failure and ventilator dependence, called *myasthenic crisis,* occurs in 15-20% of patients (27). The deficit in myasthenia is purely motor, with no sensory involvement. Deep tendon reflexes are usually preserved.

In addition to concurrent illness and surgery, several medications can precipitate or aggravate the myasthenic syndrome. The principle offenders are antibiotics (e.g., aminoglycosides, ciprofloxacin), cardiac drugs (e.g., beta-adrenergic blockers, lidocaine, procainamide, quinidine), and magnesium (28). Magnesium blocks the presynaptic release of acetyl-choline, and can be particularly detrimental in myasthenic patients.

Diagnosis

The diagnosis of myasthenia gravis is based on the characteristic pattern of muscle weakness (e.g., eyelid or extraocular muscle weakness, worse with activity) and the finding of increased muscle strength after the administration of edrophonium (Tensilon), an acetylcholinesterase inhibitor. Acetylcholine receptor antibodies can be demonstrated in the blood (by radioimmunoassay) in 85% of cases, and presence of

antibodies confirms the diagnosis (25). Once the diagnosis is confirmed, a search for associated conditions such as thymic tumors 00-20% of cases) and hyperthyroidism (5% of cases) is advised.

Treatment

The first line of therapy in myasthenia gravis is the administration of acetylcholinesterase inhibitors like **pyridostigmine** (Mestinon), which is started at an oral dose of 60 mg every 6 hours and is increased if necessary to a maximum dose of 120 mg every 6 hours. Pyridostigmine can be given intravenously to treat myasthenic crisis (the IV dose is 1/30 of the oral dose) (27,29). **Immunotherapy** is added if needed using either prednisone 0-1.5 mg/kg/day), azathioprine 0 to 3 mg/kg/day), or cyclosporine (2.5 mg/kg twice per day) (29).

In advanced cases requiring mechanical ventilation, **plasmapheresis** (to remove anti-acetylcholine receptor antibodies) is often effective in producing short-term improvement (29). **Intravenous immunoglobulin G** (0.4 to 2 g/kg/ day for 2 to 5 days) to neutra lize pathogenic antibodies is also effective (26,29). Both therapies are equally effective; however, plasmapharesis may produce a more rapid rf'sponse (29). Surgical thymectomy is often advised in patients under 60 years of age to reduce the need for immunosuppressive therapy (29).

Guillain-Barre Syndrome

The Guillain-Barre syndrome is an acute inflammatory demyelinating polyneuropathy that follows an acute infectious illness (by 1 to 3 weeks) in two-thirds of cases (30,31). The infectious agents most often associated with this disorder are *Campylobacter jejeuni* and cytomegalovirus (30). An immune etiology is suspected, and some patients have circulating antibodies to gangliosides in peripheral nerves (30).

Clinical Features

The clinical presentation is marked by paresthf'sias, diminished reflexes, and symmetric limb weakness that evolve over a period of a few days to a few weeks. Symptoms of a preceding infection usually subside before the weakness becomes apparent. Approximately 25% of cases show progression to respiratory failure requiring mechanical ventilation (30). Advanced cases can also be associated with autonomic instability and bulbar paralysis (30,32,33). The condition resolves spontaneously in approximately 80% of cases; however, residual neurological deficits are common (30).

Diagnosis and Therapy

The diagnosis is based on the clinical presf'ntation (progressive symmetric limb weakness following an acute infectious illness), the results of nerve conduction studies (slowing of nerve conduction due to demyelination), and cerebrospinal fluid analysis (elevated protein content in 80%) (30).

The treatment of Guillain-Barre syndrome mostly involves supportive care. In severe cases requiring mechanical ventilation, **plasmapheresis or intravenous immunoglobulin G** (0.4 g/kg/day for 5 days) are **equally effective in producing short-term improvement**. Immunoglobulin G is often preferred because it is easiest to administer (30). Since this disorder resolves spontaneously in most cases, careful attention to the potential complications (e.g., pneumonia, thromboembolism) is mandatory for optimal patient outcome. The respiratory management of this disorder is described later in the chapter.

Critical Illness Polyneuropathy and Myopathy

Critical illness polyneuropathy and myopathy are complications of clinical disorders that are associated with progressive and uncontrolled systemic inflammation. These conditions, which are described in Chapter 40, include the systemic inflammatory response syndrome (SIRS), severe sepsis, and multiorgan failure. Although common, these neuromuscular complications often go undetected because they are overshadowed by the more prominent clinical manifestations of the inciting conditions (34).

Clinical Features

As many as 70% of patients with SIRS or sepsis and multiple organ failure will have evidence of polyneuropathy or myopathy, and both disorders can occur in the same patient (22). Although there may be severe limb and truncal involvement, the weakness usually becomes apparent only after the underlying illness begins to resolve. In many cases, the weakness is first discovered when a patient is unable to wean from mechanical ventilation. Persistent weakness after discontinuing treatment with a neuromuscular blocking agent is another way these conditions can become apparent.

Critical Illness Polyneuropathy

Critical illness polyneuropathy is a diffuse sensory and motor axonal neuropathy that is reported in 50-70% of patients with SIRS (22,35). It is often preceded by septic encephalopathy, and the two occur together in 70% of patients (22). Bulbar weakness is uncommon and autonomic function is preserved, which helps to distinguish this condition from the Guillain-Barre syndrome (36). The onset of polyneuropathy is variable, occurring from 2 days to a few weeks after the onset of the inciting illness (37-39). Electrodiagnostic testing (with nerve conduction studies and electro-myograms) is necessary to establish the diagnosis. There is no specific treatment for this disorder, and prevention (by prompt treatment of the predisposing condition) is currently the only option. One study has shown that intensive insulin therapy (to achieve tight control of blood glucose) can reduce the incidence of critical illness polyneuropathy by 44% (40). Complete recovery is expected in 50% of cases (36). In mild

cases of polyneuropathy, recovery can be complete within a few weeks, but in severe cases, recovery can take months.

Critical Illness Myopathy

Critical illness myopathy is a spectrum of muscle disorders that present with diffuse weakness, depressed deep tendon reflexes, and mildly elevated creatine kinase levels (in 50% of cases) (24). Electrodiagnostic testing reveals a myopathy, and muscle biopsy reveals atrophy and loss of thick (myosin) filaments (24). Critical illness myopathy is observed in about one-third of patients with status asthmaticus, (particularly those receiving high-dose corticosteroids) (24). This myopathy is also more prevalent with prolonged use of corticosteroids and neuromuscular blocking agents (22,24). Like the polyneuropathy, there is no specific treatment for critical illness myopathy. Most patients with isolated critical illness myopathy make a full recovery in a few months (24).

Pulmonary Complications

The pulmonary consequences of progressive neuromuscular weakness are summarized in Table 51.4. Respiratory muscle strength must decrease considerably before pulmonary complications appear. The earliest complication is a depressed cough with difficulty clearing secretions. This can lead to aspiration and retained secretions with infection and airway obstruction. When patients are unable to swallow or clear secretions adequately, tracheal intubation is warranted. As the neuromuscular weakness progresses, atelectasis and hypoxemia become prominent, followed by alveolar hypo ventilation and progressive CO_2 retention. Hypoxemia is often a late finding, especially when patients are breathing supplemental oxygen.

One of the important points to note in Table 51.4 is the recommendation for early tracheal intubation and mechanical ventilation before

TABLE 51.4 Respiratory Consequences of Neuromuscular Weakness

Vital Capacity (mL/kg)	Consequences	Management
70	Normal respiratory muscle strength	Observe
30	Impaired cough with difficulty clearing secretions	Chest physiotherapy
25	Accumulation of secretions, with risk of infection and airways obstruction	Tracheal intubation
20	Atelectasis and progressive hypoxemia	Supplemental oxygen
10	Alveolar hypoventilation and hypercapnia	Mechanical ventilation

the appearance of respiratory failure (31,41). This is necessary in cases of neuromuscular weakness to prevent complications arising from the inability to clear respiratory secretions. The most sensitive measure of respiratory muscle strength in this situation is the maximum inspiratory pressure (Plmax) (42), which is described in Chapter 27. A Plmax <30 cm H_20 is evidence of severe respiratory muscle weakness, and is an indication for tracheal intubation and assisted ventilation.

NEUROMUSCULAR BLOCKERS

Drug-induced neuromuscular blockade is sometimes needed to manage ventilator-dependent patients who are agitated and difficult to ventilate. However, this practice has serious potential drawbacks (43,44), as described later. Overall, less than 10% of ICU patients receive these agents (45). The clinical practice guidelines for the sustained use of neuromuscular blockers in the ICU are listed in the bibliography at the end of the chapter (46,47).

Mechanisms

Neuromuscular blocking agents act by binding to nicotinic acetylcholine receptors on the postsynaptic side of the neuromuscular junction. Once bound, there are two different modes of action. The *depolarizing agents* act like acetylcholine, producing a sustained depolarization of the postsynaptic membrane that blocks subsequent muscle contraction. The *nondepolarizing agents* act by competitively inhibiting acetylcholine-induced depolarization of the post-synaptic membrane.

Neuromuscular Blockers

The neuromuscular blocking drugs that are most frequently used in the ICU are shown in Table 51.5 (46,48). All three agents in this table are nondepolarizing blockers.

Pancuronium (Pavulon) is a relatively long-acting neuromuscular blocker that was introduced for clinical use in 1972. The initial popularity of this agent has dwindled because of its long duration of action (tendency to accumulate with prolonged use) and vagolytic effect (which causes an increase in heart rate) (49). Although pancuronium can be given by continuous infusion, it is usually given as intermittent bolus doses to decrease the risk of drug accumulation. About 60% of pancuronium is excreted unchanged by the kidneys, and dosage reduction is therefore necessary in renal failure. When hepatic and renal function are intact, pancuronium is the preferred agent in the ICU (46,47).

Rocuronium (Zemuron) is a newer drug that produces a rapid onset of block and is devoid of cardiovascular side effects. Rocuronium is eliminated mostly in the bile and the dosage must be reduced in liver failure.

Cisatracurium (Nimbex) consists of a single potent isomer of its parent drug, atracurium (which consists of 10 isomers). While atracurium

TABLE 51.5 Pharmacology of Selected Nondepolarizing Neuromuscular Blockers

	Pancuronium (Pavulon)	Rocuronium (Zemuron)	Cisatracurium (Nimbex)
Initial Dose (mg/kg)	0.1	0.6-1.0	0.1-2.0
Duration (min)	60-100	30-40	35-50
Infusion (μg/kg/min)	1-2	10-12	2.5-3
Effect on Heart Rate	Tachycardia	Mild increase at high dose	None
Active Metabolite	Yes	No	Yes
Effect of Renal Failure	Prolongs effect of drug & metabolite	Minimally prolonged	None
Effect of Hepatic Failure	Mildly prolonged	Prolonged	None

can be used in the ICU, cisatracurium is preferred because: 1) it does not cause histamine release, 2) it does not cause cardiac depression, and 3) it generates less laudanosine, a metabolite that may cause neuroexcitation (50). Cisatracurium is rapidly degraded in the plasma, and it must be given by continuous infusion. The clinical effect is not prolonged by liver or kidney failure (51).

Succinylcholine (Anedine) is the only approved *depolarizing* neuromuscular blocker, and it is not included in Table 51.5 because it is used infrequently in the ICU. This agent is ultra-short acting, and is used only to facilitate endotracheal intubation. An intravenous dose of 1-2 mg/kg produces paralysis within 60 seconds, and the effect lasts for about 5 minutes. The depolarization of muscles cells produced by this agent is accompanied by potassium efflux out of muscle cells, and this can transiently raise the serum potassium by about 0.5 mEq/L (52). Life-threatening increases in serum potassium can occur when succinylcholine is given in the presence of denervation injury (e.g., head or spinal cord injury), rhabdomyolysis, hemorrhagic shock, thermal injury, and chronic immobility. Because these conditions are prevalent in ICD patients, it is wise to avoid succinylcholine in the ICU (53).

Monitoring

The standard method of monitoring drug-induced neuromuscular blockade is to apply a series of four low-frequency (2 Hz) electrical pulses (current strength 50 to 90 milliamps) to the ulnar nerve at the forearm, and observe for adduction of the thumb. Total absence of thumb adduction is evidence of excessive block. The desired goal is 1 or 2 perceptible twitches, and the drug infusion is adjusted to achieve that end-point (46,54).

Disadvantages
The following risks of neuromuscular paralysis are considerable enough to avoid this practice whenever possible. With the aggressive use of sedation and analgesia, use of neuromuscular blockers can often be avoided.

Inadequate Sedation
Neuromuscular blocking drugs do not produce analgesia or sedation and, because paralysis is an extremely frightening and even painful experience, it is imperative to establish the desired levels of sedation and analgesia *before* initiating drug-induced paralysis (44,46). Once the patient is paralyzed, liberal use of sedatives is advised to minimize the risk of awakening.

Prolonged Weakness
Neuromuscular blocking drugs can be associated with prolonged periods of muscle weakness after the drugs are discontinued. There are several possible reasons for this, including residual drug effect, and the presence of an underlying condition that predispose to neuromuscular weakness (46). Because of the risk for prolonged weakness, neuromuscular blocking drugs should be avoided (if possible) in any patient with a condition that predisposes to neuromuscular weakness (e.g., prolonged corticosteroid therapy).

Hypostatic Pneumonia
The absence of coughing during paralysis impairs the clearance of respiratory secretions. Endotracheal suction catheters are unable to reach the distal airways and prevent pooling of secretions in dependent lung regions. This can lead to *hypostatic pneumonia.*

Venous Thromboembolism
Loss of the milking action of muscle contraction on the venous return from the legs predisposes to venous thrombosis during neuromuscular paralysis. Therefore, prophylaxis for venous thrombosis (as described in Chapter 5) is mandatory during neuromuscular paralysis.

A FINAL WORD
Critical illness polyneuropathy and myopathy are common in conditions like severe sepsis that are associated with inflammatory injury to major organs. In fact, these neuromuscular disorders are probably the result of inflammatory injury involving peripheral nerves and skeletal muscle, which means they are probably part of the multiorgan failure that develops in patients with uncontrolled systemic inflammation (see Chapter 40). Like the other forms of inflammatory organ injury (e.g., acute respiratory distress syndrome) in the multiorgan failure syndrome, critical illness polyneuropathy and myopathy remain untreatable conditions that can add considerably to the morbidity and mortality of the ICU stay.

REFERENCES

Chapter 52

STROKE AND RELATED DISORDERS

The principal focus of this chapter is a cerebrovascular disorder that was first described over 2,400 years ago, and since then has suffered through a variety of poorly descriptive names like apoplexy, stroke, cerebrovascular accident (what accident?), and brain attack. Considering that this disorder is the third leading cause of death in the United States, and the number one cause of long-term disability (1,2), it deserves a more appropriate name. This chapter is devoted to the clinical presentation and early management of patients with stroke and other life-threatening cerebrovascular disorders. Several reviews on this topic are included at the end of the chapter (2-4).

DEFINITIONS
The following definitions and classifications are from the National Institute of Neurological Disorders and Stroke (5).

Stroke

Stroke is an acute brain disorder of vascular origin accompanied by neurological dysfunction that persists for longer than 24 hours (5). The neurological dysfunction is usually focal (which is typical of vascular occlusion), however, global dysfunction can occur when vascular rupture leads to hemorrhage and mass effect.

Classification of Stroke

Stroke can be classified according to its cause, as *ischemic* or *hemorrhagic* (citations specify the treatment guidelines) (1,3,5).

Ischemic stroke accounts for 80 to 88% of all strokes (6-9).

Thrombotic stroke accounts for 80% of ischemic strokes and is caused by atherosclerotic disease (3).
Embolic stroke accounts for 20% of ischemic strokes. Most emboli originate from thrombi in the left atrium (from atrial fibrillation) or left ventricle (from acute MI), but some originate from venous thrombi in the legs that reach the brain through a patent foramen ovale (10).

Hemorrhagic stroke accounts for 12-20% of all strokes.

Intracerebral hemorrhage makes up 75% of hemorrhagic strokes, and is due to rupture of a blood vessel located within the brain parenchyma (11).
Subarachnoid hemorrhage makes up 25% of hemorrhagic strokes, and is due to rupture of a blood vessel (often a saccular aneurysm) into the subarachnoid (cerebrospinal fluid) space (12,13).

Epidural and subdural hematomas are not considered to be strokes (5), and are not described in this chapter.

Transient Ischemic Attack
A *transient ischemic attack* (TIA) is an acute episode of focal loss of brain function due to ischemia that lasts less than 24 hours (5,14). The one feature that distinguishes TIA from stroke is the reversibility of clinical symptoms. Reversibility of cerebral injury is not a distinguishing feature because one-third of TIAs are associated with cerebral infarction (detected by magnetic resonance imaging) (9,15).

BEDSIDE EVALUATION
Acute stroke is a condition of ongoing ischemic injury that should be approached as a medical emergency. Each minute of ischemic stroke causes the destruction of 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated nerves (16). In light of these numbers, the popular saying *time is brain,* should be upgraded to state *time is a lot of brain!*
Stroke is primarily a clinical diagnosis (17). The presentation is characterized by one or more focal neurological deficits corresponding to the region(s) of the brain that is ischemic (4). The clinical findings and corresponding regions of ischemic brain injury are shown in Figure 52.1 (6). The following is a summary of the pertinent clinical features of acute stroke (18).

Consciousness
Most cerebral infarctions are unilateral, and thus loss of consciousness is not a common finding (19,20). The causes of altered consciousness are

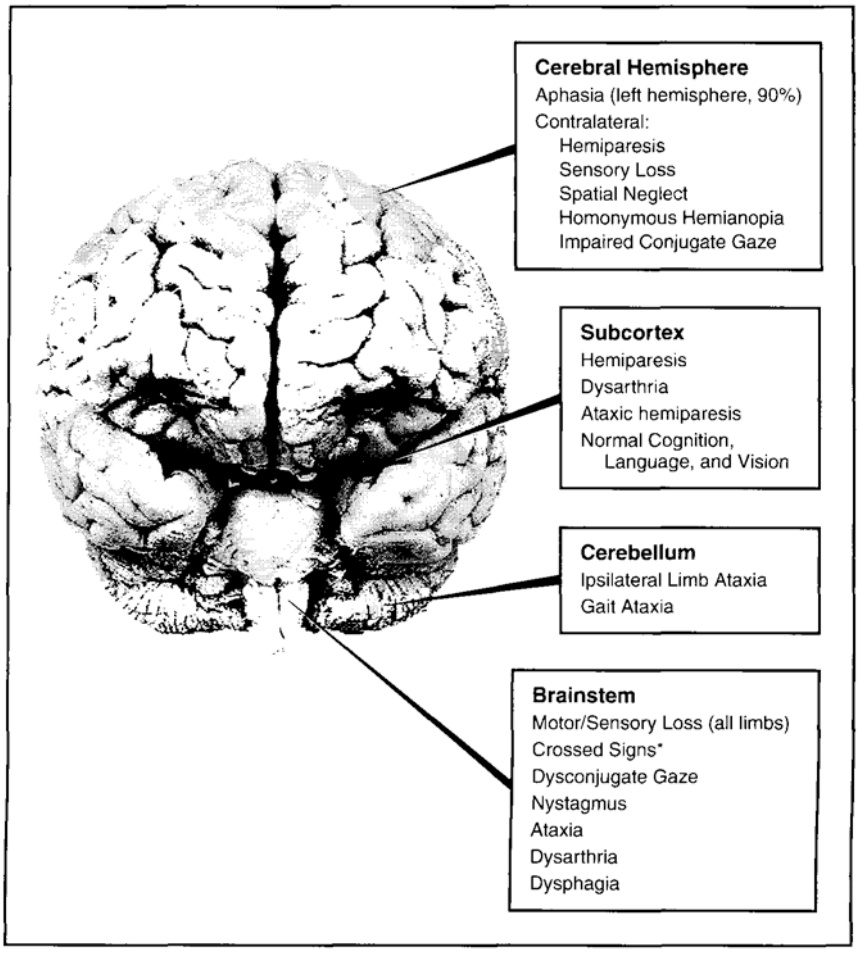

FIGURE 52.1 Neurological abnormalities and corresponding areas of ischemic brain injury. *Signs on same side of face and other side of body.

described in Chapter 50). When focal neurological deficits are accompanied by altered consciousness or coma, the most likely diagnoses are intracerebral hemorrhage, massive cerebral infarction with cerebral edema, brainstem infarction, or seizures (nonconvulsive seizures or postictal state).

Sensorimotor Function

The hallmark of ischemic or hemorrhagic injury involving the cerebral hemispheres is motor weakness and sensory loss on the contralateral side of the face and body. The presence of hemiparesis supports the diagnosis of TIA or stroke, but is not specific for these conditions. Hemiparesis has

also been described in metabolic encephalopathy due to liver failure (21), renal failure (22), and sepsis (23).

Aphasia
The left cerebral hemisphere is the dominant hemisphere for speech in 90% of subjects. Damage involving the left cerebral hemisphere produces a condition known as *aphasia,* which is defined as a disturbance in the comprehension and/or formulation of language. Patients with aphasia can have difficulty in verbal comprehension (receptive aphasia), difficulty in verbal expression (expressive aphasia), or both (global aphasia).

Dysphagia
Up to half of patients admitted to the hospital for stroke will have swallowing dysfunction (3). These patients are at risk for pulmonary aspiration and pneumonia. Because of this, these patients might benefit from oral decontamination as a preventive measure for nosocomial pneumonia (see Chapter 4).

Fever
Fever (T > 37.5°C) develops in 40% of cases of acute stroke, and usually appears in the first 24 hours after symptom onset (24,25). The severity of the fever usually correlates with severity of the stroke (25-27).

Seizures
Seizures are uncommon (5%) in the first 2 weeks after ischemic stroke (28). They often occur as a single event in the first day after stroke onset. Partial seizures are most common. (28). Primary generalized convulsive seizures and recurrent seizures (2.5%) are uncommon after stroke or TIA (28).

DIAGNOSTIC EVALUATION
Once a stroke is suspected, candidates for thrombolytic therapy must be identified, and they must be identified *quickly* because the benefit of thrombolytic therapy in ischemic stroke is confined to the first 3 hours after symptom onset (see Table 52.1) (6). The checklist in Table 52.1 contains all the elements of the evaluation for thrombolytic therapy in individual patients. Most of the evaluation involves a search for hemorrhage and other contraindications to thrombolytic therapy. The search for intracranial hemorrhage requires neuroimaging studies.

Computed Tomography
The principal role of head CT imaging in suspected stroke is to identify hemorrhage, which is an absolute contraindication to thrombolytic

TABLE 52.1 Checklist for Thrombolytic Therapy

1. *Check the **indications** below that apply:*

- [x] Patient is 18 years of age or older
- [x] Time of symptom onset can be identified accurately
- [x] Thrombolytic therapy can be started within 3 hours of symptom onset

2. *If all the boxes in Step 1 are checked, then review the **absolute contraindications** below and check the ones that apply:*

- [ ] Head CT scan today shows intracranial bleeding
- [ ] Head CT scan today shows no intracranial bleeding but the clinical presentation is suspicious for subarachnoid hemorrhage
- [ ] Head CT scan today shows multilobar infarction (hypodense area > one-third the area of the cerebral hemisphere)
- [ ] Any of the following within the past 3 months: intracranial or intraspinal surgery, serious head trauma, or a witnessed seizure
- [ ] Witnessed seizure since the onset of symptoms
- [ ] Blood pressure > 185 mm Hg (systolic) or > 110 mm Hg (diastolic)
- [ ] Arterial puncture at non-compressible site within past 7 days

Risk of hemorrhage:

- [ ] Evidence of active internal bleeding
- [ ] Patient has an arteriovenous malformation, aneurysm, or neoplasm
- [ ] Prior history of intracranial bleeding
- [ ] Laboratory evidence of a coagulopathy (e.g., platelet count <100,000/μL)
- [ ] Patient on coumadin and INR ≥ 1.7, or patient received heparin in past 48 hr and aPTT above normal range

3. *If none of the boxes in Step 2 are checked, review the **relative contraindications** below and check any that are considered an unacceptable risk:*

- [ ] Major surgery or serious trauma in past 14 days
- [ ] Gastrointestinal or urinary tract bleeding within past 21 days
- [ ] Acute MI in past 3 months or post-MI pericarditis
- [ ] Blood glucose < 50 mg/dL or > 400 mg/dL

If all boxes in step 1 are checked, and no boxes in steps 2 and 3 are checked, then give thrombolytic therapy.

From the 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 9, Adult Stroke. Circulation 2005;112:IV111–120.

therapy. The sensitivity of CT scans for intracerebral hemorrhage is almost 100%, and the sensitivity for subarachnoid hemorrhage is 90 to 95% (9). Computed tomography will also identify the occasional case of a space-occupying lesion (e.g., epidural or subdural hematoma, tumor, or abscess) (6,9).

The diagnostic yield of CT imaging is much less for infarction. Onehalf of cerebral infarcts are not apparent on CT scan (3), and the diagnostic yield is even less in the first 24 hours after symptom onset (9). An example of the influence of timing on the diagnostic yield from CT scans is illustrated in Figure 52.2 (29). Therefore, a negative CT scan, especially when performed within 24 hours after symptom onset, does not rule out the presence of cerebral infarction.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can detect 90% of strokes in the first 24 hours after symptom onset (9). The value of MRI in suspected stroke is illustrated by the case in Figure 52.3. The MRI in this figure is from a previously healthy 39-year-old woman who presented with acute onset of right arm and leg weakness. The initial CT scan was unrevealing, but the MRI reveals multiple (hyperdcnse) infarctions along the course of the left middle cerebral artery (infarctions are hypodense on CT scans, and

are hyperdense on MRI). This prompted a cerebral angiogram, which revealed probable vasculitis as a cause of the cerebral infarction.

MRI is also superior to CT imaging for detecting the following conditions: hemorrhage, subdural hematoma, aneurysms, arteriovenous malformations, microvascular disease, and venous sinus thrombosis. Because of the superior diagnostic yield, MRI is likely to replace CT imaging in the future for the early evaluation of stroke.

Because MRI uses magnetic pulses, it is contraindicated in patients with implanted pacemakers and cardioverter / defibrillators, as well as ferromagnetic implants, (e.g., some aneurysm clips, prosthetic joints, and cochlear implants). Intracoronary stents are not a contraindication to MRI imaging (30).

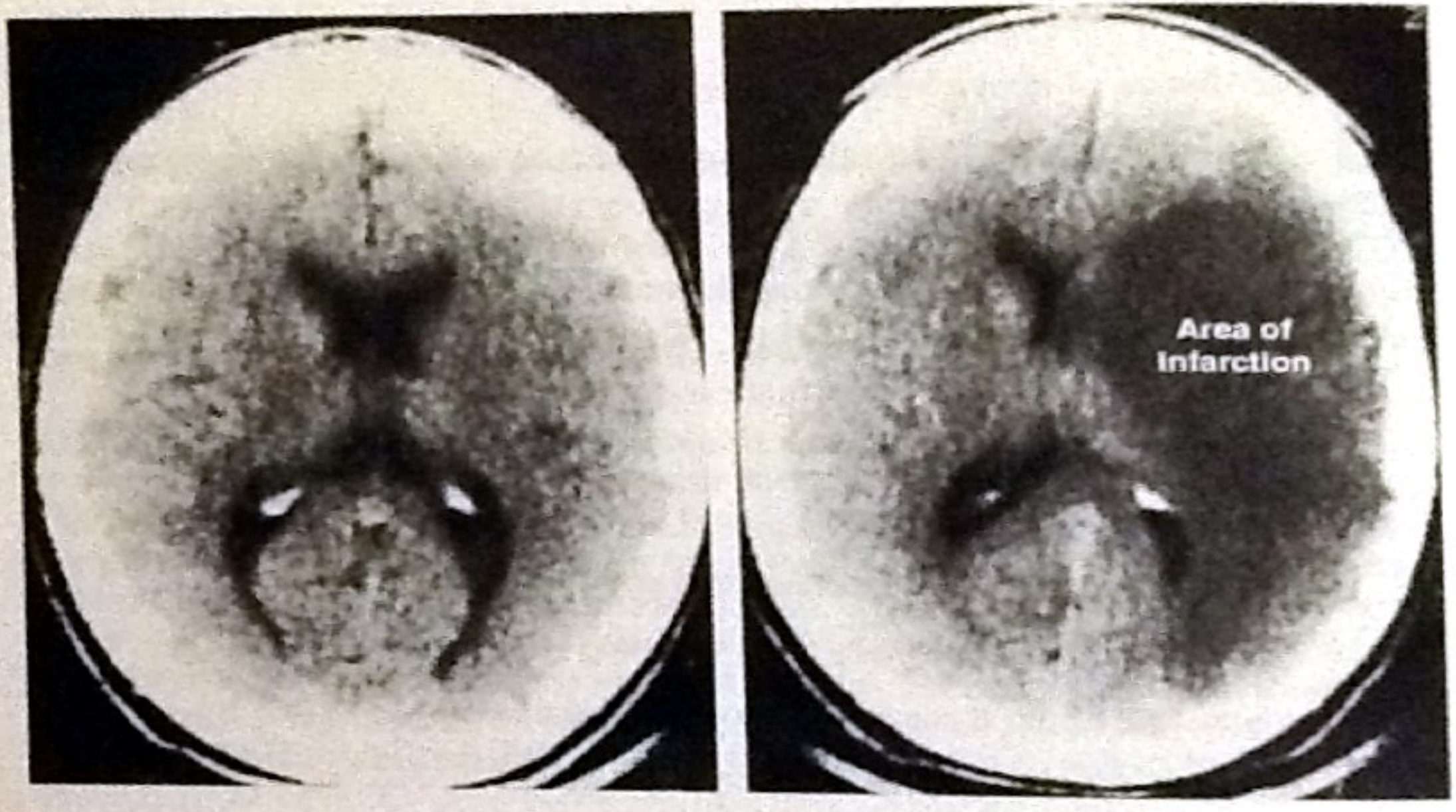

FIGURE 52.2 The influence of timing on the yield from CT scans. Both CT scans are from the same patient. The scan on the left was obtained within 24 hours after the onset of symptoms, and is unrevealing. The scan on the right was obtained 3 days later, and shows a large hypodense area on the left cerebral hemisphere. Reproduced with permission from (29). Images are digitally enhanced.

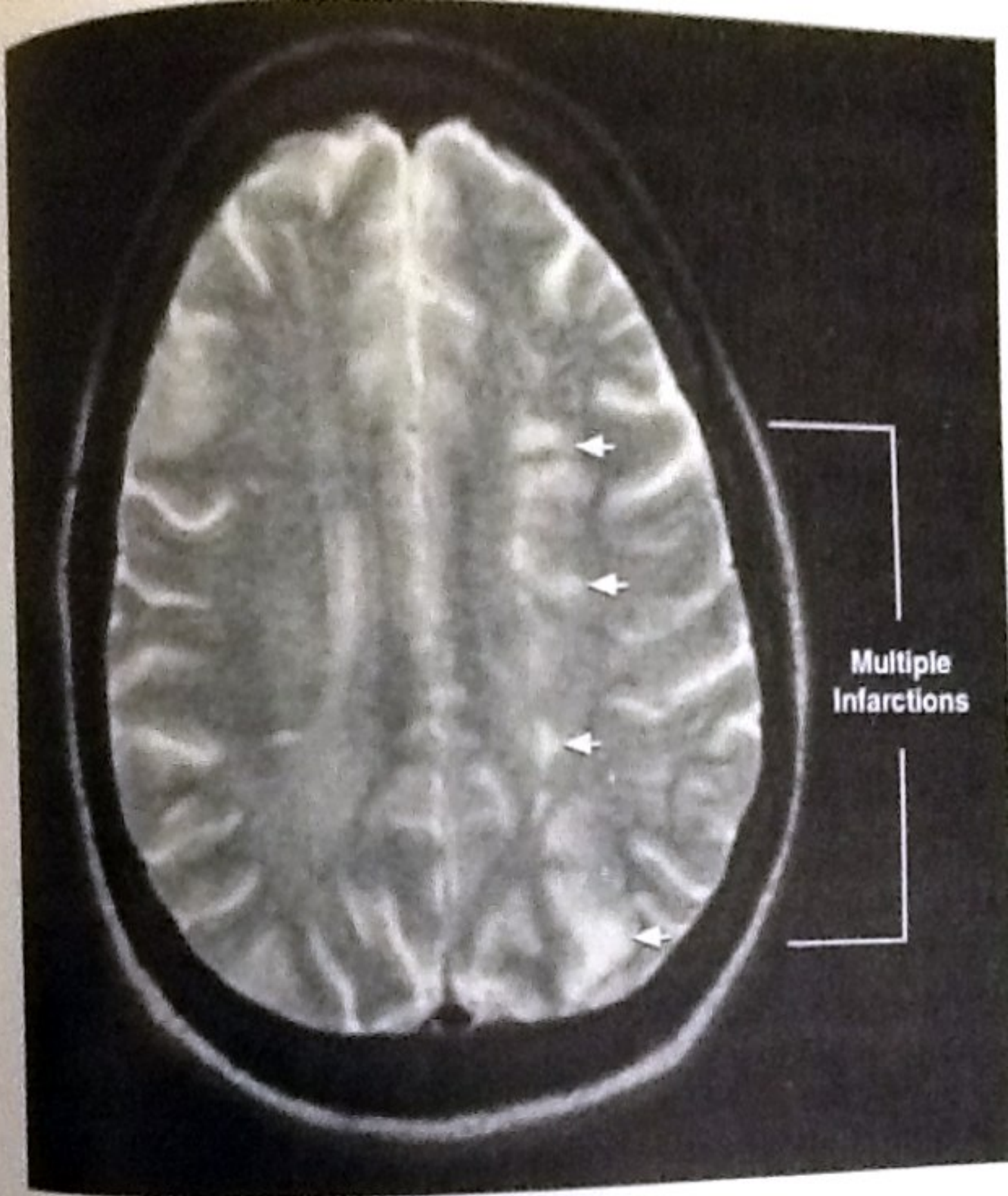

FIGURE 52.3 A T_2-weighted MRI from a 39-year-old woman with acute onset of right-sided weakness and a normal CT scan. The arrows point to hyperdense areas of infarction along the distribution of the left middle cerebral artery. Cerebral angiography revealed probable vasculitis. Case history and MRI courtesy of Dr. Sami Khella, M.D. Image digitally enhanced for clarity.

Other Diagnostic Tests

The following tests are appropriate for the indications cited.

Lumbar puncture is not indicated in most patients with suspected stroke. **It** can be useful when the CT scan reveals subarachnoid hemorrhage, or to exclude meningitis.

Echocardiography is indicated when stroke is associated with atrial fibrillation, acute MI, or left-sided endocarditis. **It** may also be indicated in stroke of undetermined etiology, and to identify a patent foramen ova le (and possible paradoxical cerebral embolism).

Electroencephalography is indicated in cases where seizures are suspected as the cause of the neurological deficits.

THROMBOLYTIC THERAPY

The popularity of thrombolytic therapy for ischemic stroke is based on a single (albeit multicenter) study showing that treatment with tissue plasminogen activator (0.9 mg/kg infused over 1 hr, max = 90 mg) improved neurological outcome if therapy was started within 3 hours after symptom onset (31). Mortality was unaffected, and the incidence of intracerebral hemorrhage associated with lytic therapy was 6.4% (10-fold greater than in the control group) (31,32). Despite the lack of survival benefit and the increased risk of intracranial hemorrhage, the Food and Drug Administration (in 1996) approved the use of tissue plasminogen activator (tPA) for acute, ischemic stroke in the first 3 hours after symptom onset. The drug approval is limited to strokes involving the anterior cerebral circulation only. The guidelines for patient management are detailed in the following references (6,7).

Where's the Beef?

The approval of thrombolytic therapy for acute stroke was heralded as a "breakthrough" in the treatment of stroke. However, the eligibility criteria for thrombolytic therapy (e.g., therapy must begin within 3 hours after symptom onset) are restrictive and, as a result, only 1-2% of patients with acute stroke (and 3-4% of patients that reach the hospital) receive tissue plasminogen activator (33,34).

The number of people who benefit from thrombolytic therapy each year can be estimated as follows (see Fig. 52.4). There are an estimated 700,000 acute strokes each year in the United States (1), and up to 88% (616,000) are ischemic strokes (1). Of these 616,000 ischemic strokes, a maximum of 2% get lytic therapy (12,320 patients) (34) (Fig. 52.4). At least nine patients need to be treated in oder to produce one beneficial neurological outcome (that would not have occurred without therapy) (32). This means that for the maximum 12,320 patients that get tPA yearly, only 1,369 patients (0.2% of all cases of ischemic stroke) will benefit from therapy each year.

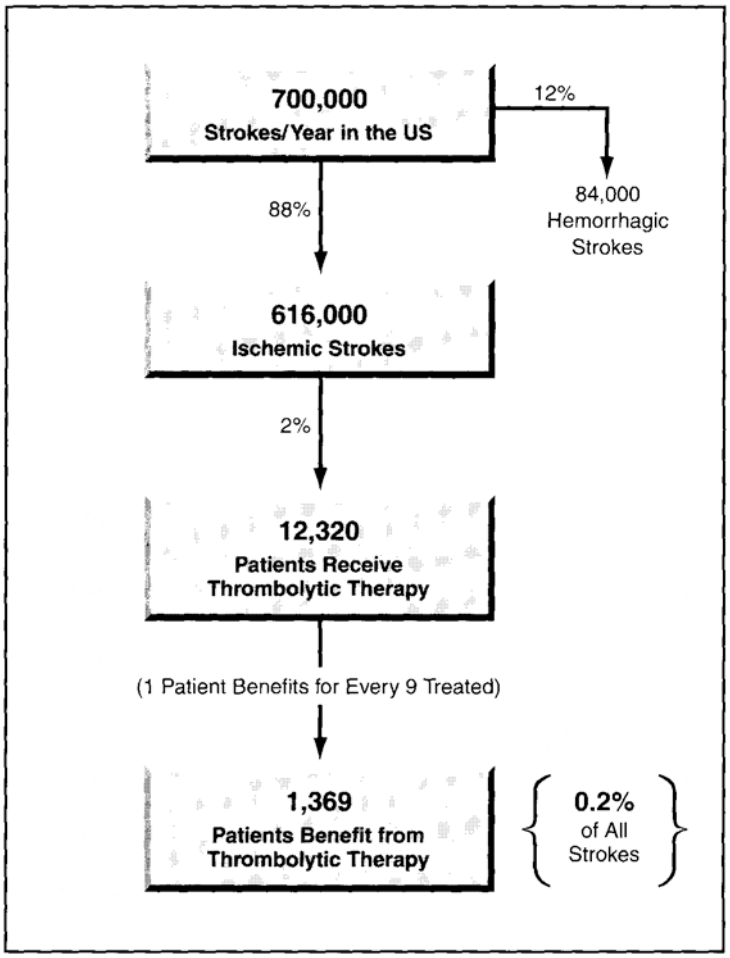

FIGURE 52.4 Impact of thrombolytic therapy in the United States each year.

ANTITHROMBOTIC THERAPY

Aspirin

Aspirin has been shown to reduce the recurrence of ischemic stroke and to reduce the mortality and long-term disability by 1 % (3,35,36). Therefore, aspirin is recommended for all cases of acute ischemic stroke (3,35,36). When thrombolytic therapy is given, aspirin should be started on the following day, otherwise the first dose of aspirin should be given after intracranial hemorrhage is ruled out by neuroimaging. The recommended dose is 160-300 mg initially (orally or per rectum) and followed by 75-150 mg daily.

Heparin
Therapeutic anticoagulation with heparin has been the traditional practice for patients with progressive ischemic stroke (37). Although early studies showed a possible benefit from this practice, these studies were not well designed, and more recent studies reveal little or no benefit from full anticoagulation in progressive ischemic stroke (37). The only role for heparin following an acute stroke is for prevention of deep vein thrombosis (see Table 5.4 for dosage).

MEDICAL MANAGEMENT
Despite the overwhelming emphasis on thrombolytic therapy in the early management of acute stroke, patients with acute stroke who are admitted to the hospital are more likely to succumb from medical complications than from complications of the stroke. About one-half of deaths following stroke are related to medical complications (2). The following is a brief description of the most troublesome medical problems in stroke victims.

Hypertension
Hypertension may be a beneficial response that helps to maintain blood flow to borderline tissue that is ischemic but not irreversibly injured *(the ischemic penumbra).* In this region, cerebral autoregulation is impaired and blood flow passively follows blood pressure (38). This dependence on blood pressure is verified by clinical studies showing that systolic blood pressure <130 mm Hg or acute lowering of blood pressure in hypertensive ischemic stroke victims is often accompanied by worsening of the neurological deficits and increased mortality (38). Other reasons to avoid antihypertensive therapy are the lack of documented benefit, and the tendency for the hypertension to resolve spontaneously in the days following an acute ischemic stroke (6,39).
Despite a lack of experimental validation, the American Stroke Association recommends antihypertensive treatment if the systolic pressure rises above 220 mm Hg or if the diastolic blood pressure rises above 140 mm Hg (6). In the setting of an acute ischemic stroke, the reduction in blood pressure should not exceed 10-15%. For intravenous therapy, labetalol (10-20 mg) and nicardipine (5 mg/hT) are preferred because they preserve cerebral blood flow (6). Sublingual nifedipine should be avoided because it may cause a rapid fall in blood pressure.

Hyperglycemia
Hyperglycemia is common in severe stroke and is associated with a poor neurological outcome (6,40). Despite the association between hyperglycemia and poor outcome, a causal relationship is unproven (6,40). Current guidelines recommend that blood glucose be maintained below 300 mg/ dL (6). Tighter glycemic control has been advocated (41); but has

unproven benefits and there is a risk for hypoglycemia. Hypoglycemia can aggravate the neurological outcome and should be avoided (6).

Fever
Patients who develop a fever following an ischemic stroke have more extensive neurological deficits and a higher mortality (26). Although a causal relationship between fever and neurological outcome is unproven, the guidelines of the American Stroke Association recommend antipyretic therapy (acetaminophen) for all patients with post-stroke fever (6,42). Fever that follows acute stroke can be infectious in origin, so a search for infection is warranted,

SUBARACHNOID HEMORRHAGE
Subarachnoid hemorrhage (SAH) is usually the result of aneurysmal rupture (43,44). Aneurysmal subarachnoid hemorrhage has a mortality rate of 50%, and one-third of survivors become functionally dependent (43,44). Although classified as a type of stroke, SAH can differ from the other types of stroke in both presentation and management (12,45,46).

Clinical Presentation
The hallmark of the clinical presentation of SAH is the acute onset of an excruciating headache. The full-blown syndrome is preceded 40% of the time by a severe but self-limited headache, called a *sentinel headache* (44), which is presumably due to aneurysm dilation or a small hemorrhagic leak. The headache of SAH is usually abrupt in onset, progressive, and worse with exertion. Other manifestations can include: nausea and vomiting, altered mental status, meningismus, focal neurological signs (especially, oculomotor or abducens nerve palsy), hemiparesis, aphasia, or leg weakness. Because of its variable clinical presentation, one-half of the cases of SAH are misdiagnosed (44).

Diagnostic Evaluation
Computer tomography (CT) of the head (unenhanced) has a 90-95% sensitivity for the detection of a SAH, and is the initial diagnostic test of choice for suspected SAH (12,43). The shortcoming of CT imaging is that it may fail to detect cases of SAH that are small or confined to the posterior fossa (where the brainstem and cerebellum are located).
The image in Figure 52.5 is an MRI from a 30 year old woman with severe and persistent headache who had a normal CT scan of the head. The MRI shows a hyperdense area (indicated by the arrows) just ventral to the pons, which represents a SAH. Thus, even though CT scans have a high sensitivity for SAH, a negative CT scan does not eliminate the possibility for SAH.

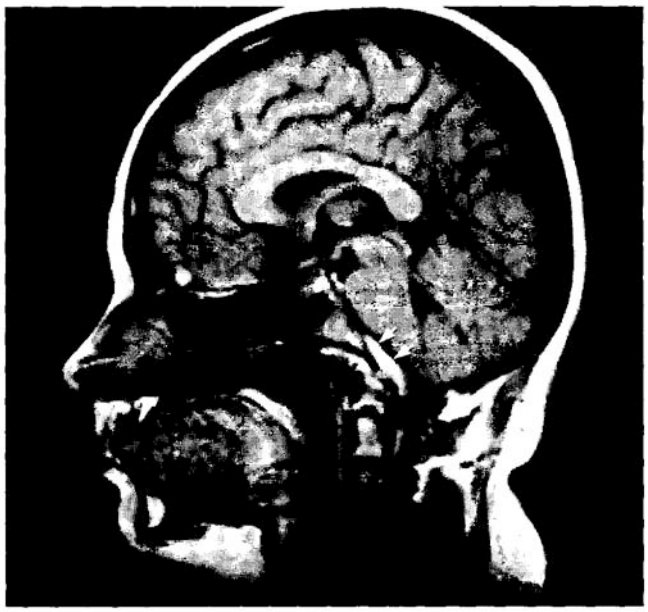

FIGURE 52.5 An MRI performed on a 30-year-old woman with severe, persistent headache and a normal CT scan of the head. Note the arrows pointing to a hyperdense area ventral to the brainstem. This represents a *prepontine subarachnoid hemorrhage*. Lumbar puncture confirmed the presence of blood in the subarachnoid space. Case history and MRI courtesy of Dr. Sami Khella, M.D.

In cases where neuroimaging is equivocal and there is a high clinical suspicion for SAH, a lumbar puncture should be performed (44).

Cerebral angiography is the gold standard for identifying the vascular lesion that is responsible for SAH. Results of angiography are needed to determine the appropriate management strategy (e.g., surgical clipping or endovascular coiling) (12).

Complications

The complications following SAH can be classified as medical, cardiac and neurological.

The most troublesome medical complications include pulmonary edema (13-23%), hyponatremia (due to SIADH or cerebral salt-wasting) (44,47,48), and deep vein thrombosis (requires prophylaxis).

The most common cardiac condition following SAH is ECG abnormalities which occur in 50-90% of cases. These abnormalities include elevation or depression of RST segment, prolongation of the QT interval, inversion of the T wave, or appearance of a U wave (49). These ECG changes can occur in the absence of coronary artery disease, and may be associated with cardiac dysfunction and release of cardiac enzymes (suggesting myocardial injury or infarction) (49). For patients who have ECG changes following SAH, cardiac troponin I levels should be measured

because elevated levels are associated with cardiac dysfunction (49). In patients without coronary artery disease, cardiac dysfunction is transient and almost always returns to baseline (49).
The neurological complications after SAH are related to three processes: recurrent hemorrhage (7%), cerebral vasospasm (46%), and hydrocephalus (20%) (44). Hydrocephalus is usually diagnosed by head CT and is treated by ventricular drainage of cerebrospinal fluid with an indwelling catheter.

Recurrent Subarachnoid Hemorrhage
In most cases of SAH, the bleeding has stopped long before the time of diagnosis. Rebleeding from an aneurysm usually occurs within the first few days and is associated with a 50% mortality (44). To prevent rebleeding, aneurysm repair is usually done in the first few days by open surgical clipping or minimally invasive endovascular coiling (50).

Cerebral Vasospasm
Spasm of the cerebral blood vessels is common following SAH and can promote cerebral ischemia or infarction. The peak incidence occurs from 4 to 12 days following SAH. The likely source of vasospasm is inflammatory mediators in subarachnoid blood (44).

NIMODIPINE. The calcium channel blocker, nimodipine, improves neurological outcome following SAH (51,52). The recommended dose is 60 mg orally every 4 hours for 21 days (44). The shortcoming with nimodipine is the "number needed to treat"; i.e., an average of 20 patients must be treated to produce one case of improved neurological outcome (53).

HYPERVOLEMIA-HYPERTENSION. Promoting cerebral blood flow is an important management goal in vasospasm following SAH. This is the basis for the traditional therapy involving induction of hypervolemia (with colloid infusion) and induced hypertension (by infusing vasoconstrictors, e.g., phenylephrine) (44,45). This therapy does not necessarily increase cerebral perfusion or reverse the signs of cerebral ischemia and it is associated with potential complications (e.g., heart failure or pulmonary edema) (45). The most important goals of therapy are to prevent hypovolemia and to maintain or augment systemic cardiac output (e.g., with dobutamine infusion).

A FINAL WORD
About 10 to 15 years ago, someone decided that myocardial infarction and cerebral infarction were similar disease processes directed at different organs. The term *brain attack* was introduced to acknowledge the similarities between cerebral infarction and myocardial infarction, and specialized *stroke units* were created to provide the same type of specialized care provided in coronary care units. The success of thrombolytic therapy in acute coronary syndromes prompted an evaluation of lytic therapy in ischemic stroke. The results of this study did not match the

success of thrombolytic therapy in acute coronary syndromes. Despite equivocal evidence of benefit, thrombolytic therapy was approved for use in acute ischemic stroke in the mid 1990s. There was, however, one catch-the treatment had to be given within three hours after the onset of symptoms. This restriction essentially eliminated any chance of a largescale impact of thrombolytic therapy on stroke. A decade has now passed and, as demonstrated in Figure 52.4, thrombolytic therapy has added only a sliver of light to the world of stroke victims. The 3-hour time restriction is blamed for the disappointing results with thrombolytic therapy, but these drugs have never shown dramatic results in the treatment of acute stroke. In fact, aspirin is more likely to produce a favorable outcome than thrombolytic therapy. The different response to thrombolytic therapy in ischemic stroke could indicate that coronary artery disease and cerebrovascular disease are not as related as presumed.
So, after all the fuss about thrombolytic therapy, it seems that the best treatment for patients with ischemic stroke is general critical care support. Just as it should be.

REFERENCES