Approach to the comatose patient

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe changes in the level of consciousness.
2. Identify the indicators of prognosis in comatose patients.
3. Use this information in a clinical setting.

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Background: **Coma is a medical emergency and may constitute a diagnostic and therapeutic challenge for the intensivist.**

Objective: **To review currently available data on the etiology, diagnosis, and outcome of coma. To propose an evidence-based approach for the clinical management of the comatose patient.**

Data Source: **Search of Medline and Cochrane databases; manual review of bibliographies from selected articles and monographs.**

Data Synthesis and Conclusions: **Coma and other states of impaired consciousness are signs of extensive dysfunction or injury involving the brainstem, diencephalon, or cerebral cortex and are associated with a substantial risk of death and disability. Management of impaired consciousness includes prompt stabilization of vital physiologic functions to prevent secondary neurologic injury, etiological diagnosis, and the institution of brain-directed therapeutic or preventive measures. Neurologic prognosis is determined by the underlying etiology and may be predicted by the combination of clinical signs and electrophysiological tests. (Crit Care Med 2006; 34:31–41)**

KEY WORDS: coma; vegetative state; hypoxic-ischemic encephalopathy; traumatic brain injury; neurologic diagnosis; outcome prediction

Coma and other states of impaired consciousness represent a severe derangement in cerebral function that may be structural or nonstructural (toxic-metabolic, pharmacologic, seizures) in origin. Many of the underlying processes leading to coma can be both life-threatening and potentially reversible with the timely institution of medical or surgical therapy. Physicians in the emergency and intensive care arena have a central role in diagnosing and treating comatose patients, the principles of which are outlined in this review.

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Disorders of Consciousness

From a clinical perspective, consciousness may be schematized as the product of two closely related cerebral functions: wakefulness (i.e., arousal, vigilance, alertness), and awareness of self or of the environment, often referred to as the "content" of consciousness (1). The content of consciousness encompasses, in turn, several other overlapping brain functions including attention, sensation and perception, explicit memory, executive function, and motivation (2). The relationship between wakefulness and awareness is hierarchical: Awareness cannot occur without wakefulness, but wakefulness may be observed in the absence of awareness (e.g., the vegetative state; discussed subsequently).

Although many aspects of consciousness remain unexplained, its neuroanatomical underpinnings have been studied extensively. Wakefulness is linked to the ascending reticular activating system (ARAS), a network of neurons originating in the tegmentum of the pons and midbrain and projecting to diencephalic and cortical structures (3, 4). Awareness is dependent on the integrity of the cerebral cortex and its subcortical connections (5). Biochemical analysis of the ARAS reveals cholinergic and glutamatergic (pon-

Table 1. Global disorders of consciousness

	Arousal	Awareness	Sleep/Wake Pattern of Cyclic Arousal	Motor Function	Respiratory Function	EEG Activity	Cerebral Metabolism (% Normal)[a]
Brain death	Absent	Absent	Absent	Absent	Absent	Electrographic silence	0
Coma	Absent	Absent	Absent	Nonpurposeful	Variable; abnormal patterns	Polymorphic delta or theta	<50
Vegetative state	Present	Absent	Present	Nonpurposeful	Present	Polymorphic delta or theta, sometimes slow alpha	40–60
Minimally conscious state	Present	Partial	Present	Intermittently purposeful	Present	Mixed theta and alpha activity	50–60
Akinetic mutism	Present	Partial	Present	Paucity of movement	Present	Diffuse nonspecific slowing	40–80
Delirium	Present	Partial	Present	Normal	Present	Diffuse nonspecific slowing	70–100
Locked-in syndrome	Present	Present	Present	Quadriplegia, anarthria. Vertical eye movement and blinking only	Present	Normal	90–100

EEG, electroencephalograph.
[a]As assessed by fluoro-deoxyglucose positron emission tomography.

tomesencephalic origin), adrenergic (locus ceruleus), serotonergic and dopaminergic (brainstem), and histaminergic (hypothalamic) pathways (5). Many of these neurons converge on the thalamus, which then sends projections to the cerebral cortex. Additional neurons of the ARAS project directly to the cerebral cortex or to other diencephalic structures such as the hypothalamus.

Pathologic changes in consciousness (Table 1) imply a significant alteration in the awareness of self and of the environment, with variable degrees of wakefulness (6). Descriptive terms such as *somnolence, stupor, obtundation*, and *lethargy* used to denote different levels of wakefulness are best avoided, given the lack of uniformity in the way these states are defined in the literature (1, 6) and the availability of objective measures such as the Glasgow Coma Scale (Table 2) (1, 7, 8).

Brain Death. Consciousness disorders must be distinguished from brain death, which is the irreversible loss of all brain and brainstem function, clinically diagnosed by demonstrating absence of consciousness, lack of motor response to noxious stimulus, and the disappearance of brainstem reflexes and respiratory drive (9). Before this determination, pharmacologic, physiologic, and metabolic causes of coma should be excluded.

Coma. Coma is characterized by the total absence of arousal and of awareness. As opposed to states of transient unconsciousness such as syncope or concussion, coma must last ≥1 hr (10). Comatose patients have no eye opening and do not speak or move spontaneously. They do not follow commands, and when provoked by a noxious stimulus their eyes remain closed, vocalization is limited or absent, and motor activity is absent or abnormal and reflexive rather than purposeful or defensive (1). Sleep-wake cycles are lacking. Coma is typically a transitional state, evolving toward recovery of consciousness, the vegetative state, the minimally conscious state, or brain death (Fig. 1). Coma is associated with injury to or functional disruption of bilateral cortical structures or of the ARAS. Lesions involving the brainstem portion of the ARAS frequently coexist with oculomotor findings and pathologic breathing patterns.

Table 2. Glasgow Coma Scale

Motor response (M)	
Follows commands	6
Localizes pain	5
Withdraws to pain	4
Flexion	3
Extension	2
None	1
Verbal response (V)	
Oriented	5
Confused speech	4
Inappropriate words	3
Incomprehensible	2
None	1
Eye opening (E)	
Spontaneous	4
To command	3
To pain	2
None	1

When assessing record best motor and response. Endotracheal tube or tracheostomy invalidates the verbal component. Coma defined as M ≤ 4, V ≤ 2, E ≤ 2 (Glasgow Coma Scale ≤ 8). Adapted from Teasdale and Jennett (8).

Vegetative State. The vegetative state (VS) is notable for preserved arousal mechanisms associated with a complete lack of self or environmental awareness (10, 11). Patients in a VS open their eyes spontaneously; however, there is no evidence of sustained visual pursuit (tracking) or visual fixation. They do not follow commands and do not move in any meaningful or purposeful manner. They evolve through temporal cycles of increased and decreased arousal akin to a "sleep-wake" pattern. Cardiovascular regulatory function, breathing patterns, and cranial

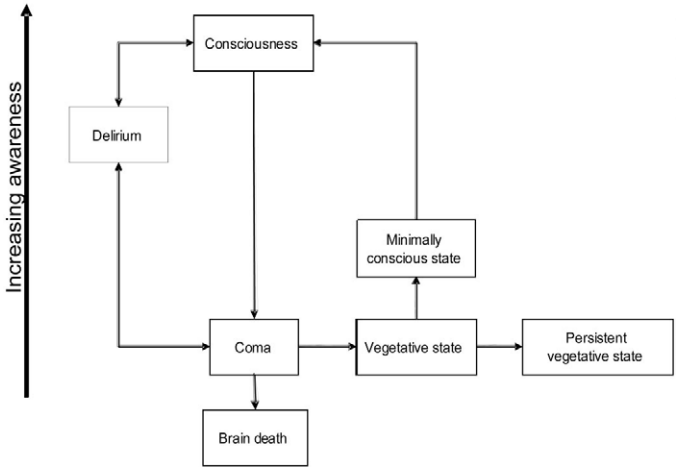

Figure 1. Spectrum of consciousness disorders.

nerves are usually intact. Although some patients who are in a VS regain partial or complete consciousness, others remain for extended periods without significant changes in their neurologic state (Fig. 1), prompting the term "persistent vegetative state" (PVS). The Multi-Society Task Force, an interdisciplinary consensus group, defined PVS as a VS present 1 month after an acute traumatic or nontraumatic injury (10). There has been debate regarding the significance of this designation, and one expert panel suggested that the term PVS be abandoned altogether (12). The VS is caused by widespread damage to bilateral cerebral hemispheres with sparing of the brainstem; trauma and hypoxic-ischemic encephalopathy are the most common acute causes of VS.

Minimally Conscious State. The minimally conscious state (MCS) describes a subset of patients who do not meet the criteria for coma or VS. Patients in MCS have a severe alteration in consciousness but demonstrate wakefulness and cyclic arousal and intermittently demonstrate self or environmental awareness, such as following of commands, the ability to signal yes/no (regardless of accuracy), intelligible speech, or purposeful behavior (13). Emergence from the MCS to higher states of consciousness is signaled by the ability to communicate reliably or use objects functionally (13). Although data are limited, it is believed that the MCS represents a greater likelihood of recovery compared with the VS. As in the VS, lesions or dysfunction associated with the MCS involve the cerebral hemispheres, with possibly greater sparing of corticocortical and cortico-thalamic connective fibers (14, 15).

Akinetic Mutism. Akinetic mutism (AM) is a state of wakefulness with limited objective evidence of awareness (16, 17). Patients with this condition generally seem unable to move or speak and have cyclic periods of increased arousal as indicated by eye opening. Some authors describe elements of visual pursuit and an intent gaze suggesting an unfulfilled "promise of speech" (18). Contrary to the MCS, there is no motor responsiveness to verbal, tactile, or noxious stimuli. A distinguishing feature from the VS is that patients with AM do not have spasticity or abnormal reflexes, suggesting relative sparing of the corticospinal tract (19). AM has been associated with bilateral medial frontal lobe (e.g., cingulate gyrus) injury or dysfunction, leading to a profound deficiency in motivation and an inability to plan and initiate activity (executive dysfunction) (17).

Delirium. Delirium is synonymous with the acute confusional state and with acute encephalopathy (20, 21). Its is characterized by an acutely developing impairment in attention, associated with changes in the level of consciousness, disorganized thinking, and a fluctuating course (22, 23). Additional features include perceptual disturbances, altered sleep-wake cycle, increased or decreased psychomotor activity, and memory impairment. Delirium is exceedingly common in hospitalized patients and particularly in the intensive care unit (24). It may precede or may evolve from other disorders of consciousness, namely coma (Fig. 1) (25). Delirium should be distinguished from dementia. Both disorders are characterized by memory impairment, but patients with dementia alone are more commonly alert and do not have the acute onset and fluctuating level of consciousness that are characteristic of a delirium (21). Delirium is frequently seen in acute toxic, metabolic, or endocrine derangements but may also result from more focal injury to the frontal or right parietal lobes (26). Nonconvulsive seizure activity and the postictal state may also mimic delirium.

Locked-In Syndrome. The locked-in syndrome (LIS) consists of quadriplegia and anarthria in the setting of preserved awareness and arousal (1). It not a consciousness disorder *per se* but may be clinically confused with one given the limited expressive capability of these patients. It is associated with acute injury to the ventral pons, just below the level of the third nerve nuclei, thus classically sparing vertical eye movements and blinking and not interfering with the more dorsally located ARAS. More rostral lesions may induce a "total" LIS, in which even eye and lid movement is lost, prohibiting all communication. Common etiologies of the LIS are pontine infarction, hemorrhage, and trauma (27). An analogous awake but de-efferented state may occur in patients with severe Guillain-Barré syndrome, botulism, and critical illness neuropathy and those receiving neuromuscular blocking agents without adequate sedation (28).

Other States of Impaired Consciousness. Several other states involve or suggest a global perturbation in consciousness. *Hypersomnia* or excessive daytime somnolence is an increase in sleeping time with preserved sleep-wake cycles, most often seen in the setting of sleep deprivation, sleep-related breathing disorders, narcolepsy, drug toxicity, metabolic encephalopathy, or damage to the ARAS (29). When aroused, patients with hypersomnia typically have a normal neurologic examination. *Catatonia* is a complication of psychiatric illnesses such as severe depression, bipolar disorder, or schizophrenia, in which patients have open eyes but do not speak or move spontaneously and do not follow commands, with an otherwise normal neurologic examination and an electroencephalogram showing low voltage but no slowing (21, 30). *General anesthesia* and *barbiturate coma* are pharmacologically induced states of decreased arousal and awareness, associated with minimal or absent responses to noxious (surgical) stimuli and prominent brainstem dysfunction and respiratory depression (31). Generalized convulsive or complex partial *sei-*

Table 3. Etiology of coma and altered consciousness

I. Primary cerebral disorders
Bilateral or diffuse hemispheric disorders
Traumatic brain injury (contusions, diffuse axonal injury)
Ischemic (watershed, cardioembolism, vasculitis, hypercoagulable disorder)
Hemorrhagic (subarachnoid hemorrhage, intraventricular hemorrhage)
Hypoxic-ischemic encephalopathy
Cerebral venous thrombosis
Malignancy
Meningitis; encephalitis
Generalized or complex partial seizures; status epilepticus (convulsive, nonconvulsive)
Hypertensive encephalopathy
Posterior reversible encephalopathy syndrome
Acute disseminated encephalomyelitis
Hydrocephalus
Unilateral hemispheric disorders (with displacement of midline structures)
Traumatic (contusions, subdural hematoma, epidural hematoma)
Large hemispheric ischemic stroke
Primary intracerebral hemorrhage
Cerebral abscess
Brain tumor
Brain stem disorders (pons, midbrain)
Hemorrhage, infarction, tumor, trauma
Central pontine myelinolysis
Compression from cerebellar infarct, hematoma, abscess, tumor
II. Systemic derangements causing coma
Toxic
Medication overdose/adverse effects (opioids, benzodiazepines, barbiturates, tricyclics, neuroleptics, aspirin, selective serotonin reuptake inhibitors, acetaminophen, anticonvulsants)
Drugs of abuse (opioids, alcohol, methanol, ethylene glycol, amphetamines, cocaine)
Exposures (carbon monoxide, heavy metals)
Metabolic
Systemic inflammatory response syndrome-sepsis
Hypoxia; hypercapnia
Hypothermia
Hypoglycemia; hyperglycemic crises (diabetic ketoacidosis, nonketotic hyperosmolar hyperglycemic state)
Hyponatremia, hypernatremia
Hypercalcemia
Hepatic failure
Renal failure
Wernicke's encephalopathy
Endocrine
Panhypopituitarism
Adrenal insufficiency
Hypothyroidism; hyperthyroidism

zures or a resulting postictal state may also lead to altered consciousness.

Etiology and Pathogenesis

Common causes of coma are traumatic brain injury (TBI), hypoxic-ischemic encephalopathy (HIE), drug overdose, ischemic stroke, intracranial hemorrhage, central nervous system infections, and brain tumors. From a pathophysiologic standpoint, coma may be viewed as the expression of a) primary insults to the cerebral cortex, diencephalic structures, midbrain or rostral pons; and b) secondary cerebral manifestations of systemic toxic, metabolic, or endocrine derangements (Table 3) (1, 32).

To affect consciousness, lesions of the cerebral cortex must involve both hemispheres or must be unilateral lesions large enough to cause displacement of midline structures (shift) (1). Brainstem and diencephalic lesions resulting in coma may be comparatively small; however, they must also involve bilateral structures (4). Compartmental shift of sufficient magnitude will disrupt the structural integrity or function of contralateral reticulothalamic or thalamocortical fibers, impairing the ARAS and its projections. Shift may also cause central or tentorial herniation with compression of the midbrain, compromising more proximal elements of the ARAS (32).

The pathophysiology of toxic and metabolic coma is specific to the underlying cause and in many instances incompletely understood (33). In a simplified view, these conditions have been linked to an interruption in the delivery or utilization of oxygen or substrate (hypoxia, ischemia, hypoglycemia, carbon monoxide), alterations in neuronal excitability and signaling (seizures, acidosis, drug toxicity), or changes in brain volume (hypernatremia, hyponatremia). The degree of neurologic impairment is related to the time course of the underlying cerebral pathology. Thus, an acute hemispheric or brainstem hemorrhage with mass effect will be associated with depressed consciousness, whereas a slowly developing brain tumor of identical location and volume may be asymptomatic. A similar observation can be made for metabolic changes, such as acute vs. progressive hyponatremia.

Approach to the Comatose Patient

Disorders of consciousness such as coma are potentially life threatening and

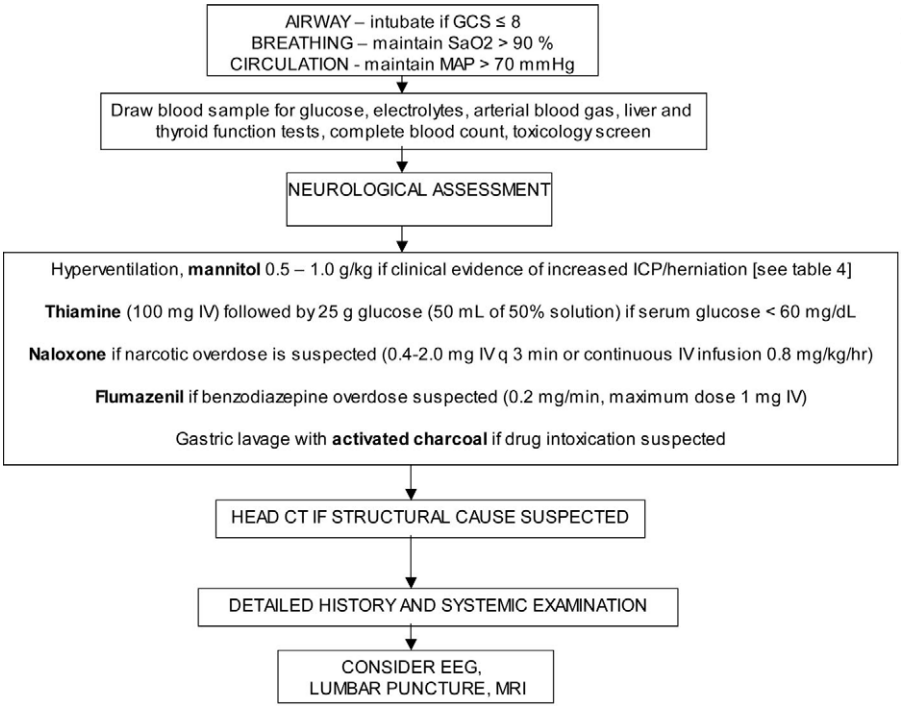

Figure 2. Algorithm for initial emergent management of the comatose patient. *GCS*, Glasgow Coma Scale; *MAP*, mean arterial pressure; *ICP*, intracranial pressure; *IV*, intravenous; *CT*, computed tomography; *EEG*, electroencephalograph; *MRI*, magnetic resonance imaging. Adapted from Reference 122.

warrant a rapid and structured approach. A basic sequence of steps is outlined hereafter. These include stabilization of vital physiologic functions, performing a focused neurologic examination, targeted diagnostic tests, and when available the institution of specific therapeutic measures (Fig. 2).

Initial Stabilization. As in any medical or surgical emergency, initial steps should be directed to ensuring adequacy of airway, breathing, and circulatory function. In patients who are comatose from TBI, or in whom the trauma cannot be ruled out as an etiological factor, the neck should be immobilized until cervical spine instability has been ruled out by clinical examination and appropriate imaging (34). Efforts should be made to swiftly identify the causes of, and correct, systemic derangements such as hypertension, hypotension, hypoxemia, anemia, acidosis, hypothermia, hyperglycemia, and hyperthermia.

Systemic Derangements. The relationship of acute neurologic disorders with derangements in circulatory and respiratory function is complex, and it is frequently not possible at the outset to accurately determine whether the systemic derangement occurred secondary to coma, was a cause of it, or was independent of it. *Hypertension* in the comatose patient suggests elevated intracranial pressure, drug overdose (amphetamines, cocaine), or hypertensive encephalopathy, but more frequently hypertension is a nonspecific hyperadrenergic response to an acutely evolving intracranial or systemic process (35). *Hypotension and shock* in the comatose patient usually reflect nonneurogenic mechanisms of circulatory failure but may also be a consequence of severe brain damage ("neurogenic stunned myocardium") (36). *Acute respiratory failure* in the comatose patient may occur secondary to airway obstruction, pulmonary aspiration, acute lung injury, or lesions affecting the pontine and medullary respiratory centers. Acute central nervous system insults have been linked to "neurogenic pulmonary edema," characterized by severe hypoxemia and protein-rich diffuse alveolar exudates (37). Coma may also represent a consequence of hypercapnic or hypoxemic respiratory failure, suggesting a vicious cycle mutually reinforcing brain and respiratory dysfunction.

The importance of appropriately treating systemic derangements is underscored by studies demonstrating that neurologic outcomes are substantially worse in patients with TBI who develop hypotension and/or hypoxia (38–41). Similar observations have been made in patients with ischemic stroke (42).

Neurologic Evaluation. The goal of the neurologic examination is to recognize the type of consciousness disorder and make inferences about its etiology. Essential neuroanatomically localizing information may be gleaned by a relatively rapid survey, which should include the level of consciousness (wakefulness), cranial nerve examination, motor examination, and respiratory pattern (1). Additional clues may be sought by examining the head and neck (e.g., meningismus), the optic fundi (e.g., subhyaloid hemorrhage in subarachnoid hemorrhage), and the skin (e.g., purpuric lesions in meningococcal meningitis) (32, 43). An important early step is to differentiate patients who have a structural cause of coma from those with a metabolic one. Structural causes are indicated by the presence of lateralizing deficits and a rostrocaudal progression of brainstem dysfunction (Tables 4 and 5). The presence of involuntary movements (seizures, myoclonus, asterixis), especially if generalized, suggests a metabolic etiology.

Level of Consciousness. The patient should be inspected for spontaneous body position, motor activity, eye opening, or verbalization. Purposeful movements (e.g., reaching for endotracheal tube) and comfort postures (e.g., crossing the legs) are signs of cortical integration. The response to stimuli of graded intensity should then be observed, starting with verbal commands, progressing to tactile cues and finally to noxious provocation. Noxious stimuli should be delivered without inducing tissue trauma and with regard to the possibility of conscious pain perception; preferable sites are the nail-bed and the notch of the supra-orbital nerve.

The Glasgow Coma Scale (GCS) (Table 2) was initially devised for patients with TBI (8) but has gained widespread acceptance as a bedside tool for evaluating the level of consciousness in virtually all acutely ill patients (44). It has good interobserver reliability (45) and is a powerful predictor of survival and neurologic outcomes after head trauma (46–49), nontraumatic coma (50), ischemic stroke (51, 52), subarachnoid hemorrhage (53), intracerebral hemorrhage (54, 55), and meningitis (56). The GCS is also an independent predictor of survival in the general critically ill population (57) and has been incorporated into a number of widely used prognostic intensive care

scoring systems (58–64). Not withstanding, the GCS has several important limitations (44, 65, 66). Subtle alterations in wakefulness and brainstem findings may not be captured by the GCS. A full GCS cannot be obtained in patients who are endotracheally intubated, are sedated, or have craniofacial trauma or in patients with dominant hemisphere lesions and aphasia. Midrange scores (6–12) may result in different combinations of the three components yielding equivalent total scores that do not reflect the same degree of unconsciousness (65, 67). Finally, differences in the higher GCS range (13–15) correlate poorly with outcome and neuroimaging findings (68, 69).

Cranial Nerve Examination. Examination of the eyes may yield valuable information about the level of brainstem disease causing coma, given the proximity of centers governing eye movement, pupillary function, and elements of the ARAS. Completely normal pupillary function and eye movements suggest that the lesion causing coma is rostral to the midbrain (70). Detection of brainstem injury may also aid in prognostication (discussed subsequently).

Table 4. Signs of intracranial hypertension and associated herniation syndromes

Sign	Mechanism	Type of Herniation
Coma	Compression of midbrain tegmentum	Uncal, central
Pupillary dilation	Compression of ipsilateral third nerve	Uncal
Miosis	Compression of the midbrain	Central
Lateral gaze palsy	Stretching of the sixth nerves	Central
Hemiparesis[a]	Compression of contralateral cerebral peduncle against tentorium	Uncal
Decerebrate posturing	Compression of the midbrain	Central, uncal
Hypertension, bradycardia	Compression of the medulla	Central, uncal, cerebellar (tonsillar)
Abnormal breathing patterns	Compression of the pons or medulla	Central, uncal, cerebellar (tonsillar)
Posterior cerebral artery infarction	Vascular compression	Uncal
Anterior cerebral artery infarction	Vascular compression	Subfalcine (cingulate)

[a]Hemiparesis will occur ipsilateral to the hemispheric lesion (false-localizing sign).

Unilateral pupillary dilation in the comatose patient is evidence of oculomotor nerve compression from ipsilateral uncal herniation until demonstrated otherwise. This presentation may also occur in patients with posterior communicating artery aneurysmal rupture. Bilateral dilated pupils that do not react to light are a sign of extensive midbrain injury, central herniation, drug intoxication (tricyclic antidepressants, anticholinergic agents, amphetamines, carbamazepine), or brain death. Unilateral miosis is suggestive of Horner's syndrome due to sympathetic denervation. Bilateral miosis is seen with lesions in the pontine tegmentum, opioid overdose, and cholinergic toxicity (organophosphates and other cholinesterase inhibitors).

Abnormalities of eye position and movement may be informative. Conjugate lateral deviation of the eyes is a sign either of an ipsilateral hemisphere lesion, a contralateral hemisphere seizure focus, or damage involving the contralateral pontine horizontal gaze center (parapontine reticular formation). Lateral gaze palsy may signal central herniation with compression of bilateral sixth nerves. Tonic downward deviation of gaze is suggestive of injury or compression involving the thalamus or dorsal midbrain such as may occur with acute obstructive hydrocephalus or midline thalamic hemor-

Table 5. Brainstem reflexes in the comatose patient

	Examination Technique	Normal Response	Afferent Pathway	Brainstem	Efferent Pathway
Pupils	Response to light	Direct and consensual pupillary constriction	Retina, optic nerve, chiasm, optic tract	Edinger-Westphal nucleus (midbrain)	Oculomotor nerve, sympathetic fibers
Oculocephalic	Turn head from side to side	Eyes move conjugately in direction opposite to head	Semicircular canals, vestibular nerve	Vestibular nucleus. Medial longitudinal fasciculus. Parapontine reticular formation (pons)	Oculomotor and abducens nerves
Vestibulo-oculocephalic	Irrigate external auditory canal with cold water	Nystagmus with fast component beating away from stimulus	Semicircular canals, vestibular nerve	Vestibular nucleus. Medial longitudinal fasciculus. Parapontine reticular formation (pons)	Oculomotor and abducens nerves
Corneal reflex	Stimulation of cornea	Eyelid closure	Trigeminal nerve	Trigeminal and facial nuclei (pons)	Facial nerve
Cough reflex	Stimulation of carina	Cough	Glossopharyngeal and vagus nerves	Medullary "cough center"	Glossopharyngeal and vagus nerves
Gag reflex	Stimulation of soft palate	Symmetric elevation of soft palate	Glossopharyngeal and vagus nerves	Medulla	Glossopharyngeal and vagus nerves

rhage. Tonic upward gaze has been associated with bilateral hemispheric damage. Ocular bobbing, a rapid downward jerk followed by a slow return to midposition, is indicative of pontine lesions. Rapid intermittent horizontal eye movements suggest seizure activity.

Integrity of the brainstem may be further ascertained by eliciting specific reflexes (Table 4). Disappearance of brainstem reflexes may also aid in prognostication (45) (discussed subsequently).

Motor Examination. Movements may be classified as involuntary, reflexic, or purposeful. Involuntary movements include seizures, myoclonus, or tremor (e.g., toxic-metabolic encephalopathy). Reflexes are stereotypical responses of the extremities evoked in patients who lack descending hemispheric modulation of motor function. Purposeful movements (e.g., localization) imply cortical processing of environmental variables.

Extensor ("decerebrate") posturing is characterized by adduction, extension, and pronation of the upper extremities and extension of the lower extremities; it is indicative of injury to the caudal diencephalon, midbrain, or pons. Flexor ("decorticate") posturing involves flexion and adduction of arms and wrists with extension of lower extremities; it suggests hemispheric or thalamic damage, with sparing of structures below the diencephalons (1).

Respiratory Pattern. Coma has been associated with disordered breathing patterns, reflecting injury to brainstem respiratory centers or interference with suprabulbar regulation of these sites (1, 71). Circulatory or respiratory failure, toxic-metabolic disorders, drugs used for sedation or analgesia, and mechanical ventilation may also contribute to abnormal breathing, limiting the inferential value of specific patterns. *Cheyne-Stokes respiration* denotes a cyclic pattern of alternating hyperpnea and apnea. It is seen in patients with a bilateral hemispheric or diencephalic insult but may also be present in congestive heart failure, chronic obstructive pulmonary disease, and sleep apnea. *Hyperventilation* has been linked to injury in the pontine or midbrain tegmentum; however, it can also result from respiratory failure, hemodynamic shock, fever, sepsis, metabolic disarray, and psychiatric disease. *Apneustic breathing* is characterized by a prolonged pause at the end of inspiration and indicates lesions of the mid- and caudal portions of the pons. *Ataxic breathing* is irregular in both rate and tidal volume and suggests damage to the medulla.

Diagnostic Tests. Patients with coma should be placed on monitors including pulse oximetry, blood pressure, and electrocardiogram, and blood should be immediately sent for glucose, electrolytes, and arterial blood gas analysis. Routine serum tests of liver, renal, thyroid, and adrenal function and urine toxicology screens should be obtained without delay.

Computed tomography (CT) of the brain is warranted in virtually all patients with an acute onset of unexplained coma. CT will readily identify intracranial hemorrhage, hydrocephalus, brain edema, and compartmental shift and may suggest stroke, abscess, or tumor. CT is unrevealing in most instances of hypoxic-ischemic or toxic-metabolic coma. Also, the usefulness of CT in patients who become comatose during the course of a critical illness is unclear. One study found that CT was unlikely to reveal abnormalities in intensive care unit patients who did not have new neurologic deficits or seizures (72). In each case, the anticipated benefit of CT in terms of actionable information should be carefully weighed against the risks of transporting a critically ill patient outside the intensive care unit.

Magnetic resonance imaging (MRI) should be sought in patients with unexplained coma and normal or equivocal CT findings. MRI is highly sensitive to acute ischemic stroke, intracerebral hemorrhage, cerebral venous sinus thrombosis, brain edema, brain tumor, inflammatory processes, and cerebral abscess. MRI is more sensitive than CT to diffuse axonal injury, a pattern of damage seen in TBI patients (73, 74). Studies in encephalopathic or comatose patients with sepsis or after cardiac surgery have found that MRI may be highly sensitive for the detection of lesions not suspected by clinical examination or CT (75–78).

Lumbar puncture and cerebrospinal fluid analysis should be considered in comatose patients with a suspected infectious or inflammatory central nervous system condition (79). However, in immunologically competent critically ill patients being worked up for fever and encephalopathy who have not undergone a recent neurosurgical procedure, the diagnostic yield of this test is low (80, 81). Patients with alterations in consciousness should undergo CT of the head before lumbar puncture to identify occult intracranial abnormalities that might cause brain herniation after removal of cerebrospinal fluid (82).

Electroencephalography (EEG) is frequently indicated in patients with unexplained coma as it may diagnose clinically occult seizure activity and in particular nonconvulsive status epilepticus. Recent studies indicate that nonconvulsive status epilepticus is present in 8–19% of patients who undergo EEG as part of the workup for an unexplained decrease in level of consciousness (83–85). The specificity of EEG for the etiological diagnosis of nonepileptic causes of coma is low; however, certain characteristic abnormalities have been described. In patients with coma of metabolic origin, a generic pattern of diffusely decreased frequency and increased amplitude has been described, often in association with "triphasic waves" (86). Some comatose patients have an EEG that superficially resembles an awake (alpha) pattern. This "alpha-coma" is most commonly seen in patients with extensive damage or dysfunction involving the brainstem or cerebral cortex and generally carries a poor prognosis (87). Finally, herpesvirus encephalitis has been associated with changes such as periodic sharp waves or epileptiform discharges (88, 89). Although the diagnostic capabilities of EEG are disappointing, it has emerged as a valuable tool in the prognostication of comatose patients (discussed subsequently).

Prognosis

Outcomes after coma include death, VS, various degrees of functional impairment, and complete neurologic recovery. Such categories have been formalized in scoring systems such as the Glasgow Outcome Scale (GOS) (90) (Table 6) and extended GOS (91). There are many other outcomes of coma including nonvegetative disorders of awareness (e.g., MCS, AM) and gradations of cognitive dysfunction that are not captured by systems such as the GOS (92). Nevertheless, the GOS is widely used by clinical investigators in both traumatic and nontraumatic coma.

The prediction of neurologic outcome is a central concern in the management of patients with coma. Surveys indicate that many individuals would prefer death to the prospect of living in a vegetative or highly dependent state (93). Prognostic information, when available, provides a rational basis for decision making about

Table 6. Glasgow Outcome Scale

1	Death	
2	Persistent vegetative state	Patient exhibits no obvious cortical function.
3	Severe disability	(Conscious but disabled). Patient depends on others for daily support due to mental or physical disability or both.
4	Moderate disability	(Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes
5	Good recovery	Resumption of normal activities even though there may be minor neurological or psychological deficits.

Adapted from Jennett and Bond (90).

therapeutic intensity, withdrawal of life support, and rehabilitation (94). Prognostication of comatose patients is based on a consideration of etiology, clinical signs, electrophysiology, neuroimaging, and biochemical data (95).

Etiology. The prognosis of coma is determined in large part by the underlying etiology. It is widely believed that toxic/metabolic coma carries a better prognosis than coma of structural origin; however, direct evidence demonstrating this is limited. On the other hand, the better prognosis of traumatic vs. anoxic coma is supported in a number of studies and two recent systematic reviews (96, 97). In adults with PVS secondary to TBI who were reevaluated at 1 yr, the proportion with a good recovery was 7%, moderate disability 17%, severe disability 28%, PVS 15%, and dead 33% (96). In patients with nontraumatic PVS (principally HIE), these outcomes were significantly worse (respectively 1%, 3%, 11%, 32%, and 53%) (96). Younger age and better general health of TBI patients may account for some of this difference.

Clinical Signs. Clinical signs that correlate with poor prognosis after coma include the motor component of the GCS (46, 47, 50, 51, 53, 55, 56), the length of time a patient remains in coma (97, 98), and signs of brainstem damage. In two separate systematic reviews of postanoxic coma, absent motor responses (GCS motor score 1) on day 3 were highly predictive of poor outcome (death or VS) (45, 99). Absent pupillary responses on day 1 (45) or 3 (99) and absent corneal reflexes on day 1 (45) were also strongly correlated with poor outcome. Clinical signs appeared to be less accurate in the prediction of outcome after TBI (100).

Electrophysiologic Tests. Electrophysiologic tests that have been used for predicting coma outcome include EEG, somatosensory evoked potentials (SSEP), transcranial motor evoked potentials, brainstem auditory evoked potentials (BAEP), and event-related potentials (86, 101). In patients with postanoxic coma, meta-analysis revealed that EEG with an isoelectric or burst-suppression pattern was independently associated with poor outcome (99). A recent systematic review implied that in patients with an alpha-coma after HIE or TBI, mortality rate was 61–90%, whereas mortality rate was 27% when alpha-coma was metabolic in origin (87). Although it remains a dependable tool for epilepsy assessment, EEG is limited by its high sensitivity to the electrical environmental noise, its alteration by sedative drugs, and its inability to test the brainstem.

Data from SSEP are strongly predictive of outcome. A systematic review revealed that among comatose patients with bilaterally absent cortical SSEP, the incidence of death or VS was 100% after HIE, 99% after intracranial hemorrhage, 95% after TBI, and 93% in children and adolescents <18 yrs old with coma of diverse etiologies (102). These results were consistent with the meta-analysis that concluded from a review of 33 studies that bilateral absence of cortical SSEP within the first week after anoxic coma was 100% specific in identifying patients with poor outcome (99). Most studies of BAEP to assess prognosis after coma were conducted with patients with TBI (101). A pooled analysis demonstrated that of 107 patients with absence of peak V (generated in the upper pons and in the midbrain) on BAEP recorded 1–59 days after TBI, 106 were dead or vegetative at 3–12 months follow-up (100). At our institution, BAEP and SSEP are obtained in selected comatose patients in whom prognosis is not readily predictable from clinical parameters alone.

Neuroimaging. Neuroimaging is essential to coma diagnosis and may have prognostic value. In patients with traumatic coma, patterns on CT that have been associated with worse neurologic outcome include lesions in the brainstem, encroachment of the basal cisterns, and diffuse axonal injury (103–108). CT findings are also predictive of outcome in comatose patients with intracerebral hemorrhage (55) and subarachnoid hemorrhage (109). However, when compared with electrophysiologic and clinical variables, the predictive value of CT is reported to be low (110). MRI in comatose patients may disclose pathologic changes of prognostic importance (73, 74, 111). In a study of patients with posttraumatic PVS, Kampfl et al. (112) assessed the relationship between MRI findings and outcome at 12 months. They noted that lesions in the corpus callosum and dorsolateral brainstem were highly predictive of nonrecovery, whereas initial GCS and pupillary findings were not (112). A relationship between MRI abnormalities and outcome is also suggested in comatose patients following ischemic stroke (113) and hypoxic-ischemic injury (114).

Biochemical Markers. The presence of brain-specific molecules in the blood or cerebrospinal fluid has been postulated to reflect the severity of brain damage. Molecules that have been studied in the prognostic evaluation of coma include neuron specific enolase (115–118), s100 beta (118), glial fibrillary acidic protein (117, 119), and the BB isoform of creatine kinase (120). Although sensitive to brain injury, the specificity and predictive value of these tests have been insufficient when compared with clinical variables and studies such as SSEP (101, 121, 122).

CONCLUSIONS

The goal of acute care of patients with coma is to maximize the likelihood of neurologic recovery. Initial resuscitative steps should be as in any other medical emergency. Subsequent therapeutic intervention is dependent on the underlying etiology, and the clinician must rapidly integrate clinical examination, laboratory, and imaging data in the formulation of a presumptive diagnosis. Prediction of outcome may be accomplished by clinical examination and electrophysiological tests.

Management of impaired consciousness includes prompt stabilization of vital physiologic functions to prevent secondary neurologic injury, etiological diagnosis, and the institution of brain-directed therapeutic or preventive measures.

REFERENCES

1. Plum F, Posner JB: The Diagnosis of Stupor and Coma. Contemporary Neurology Series 19. Third Edition. Philadelphia, Davis, 1980
2. Young GB, Pigott SE: Neurobiological basis of consciousness. *Arch Neurol* 1999; 56: 153–157
3. Moruzzi G, Magoun HW: Brain stem reticular formation and activation of the EEG. 1949. *J Neuropsychiatry Clin Neurosci* 1995; 7:251–267
4. Parvizi J, Damasio AR: Neuroanatomical correlates of brainstem coma. *Brain* 2003; 126:1524–1536
5. Zeman A: Consciousness. *Brain* 2001; 124: 1263–1289
6. Laureys S, Owen AM, Schiff ND: Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 2004; 3:537–546
7. Bateman DE: Neurological assessment of coma. *J Neurol Neurosurg Psychiatry* 2001; 71(Suppl 1):i13–i17
8. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; 2:81–84
9. Wijdicks EF: The diagnosis of brain death. *N Engl J Med* 2001; 344:1215–1221
10. Medical aspects of the persistent vegetative state (1): The Multi-Society Task Force on PVS. *N Engl J Med* 1994; 330:1499–1508
11. Jennett B, Plum F: Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 1972; 1:734–737
12. Giacino J, Whyte J: The vegetative and minimally conscious States: current knowledge and remaining questions. *J Head Trauma Rehabil* 2005; 20:30–50
13. Giacino JT, Ashwal S, Childs N, et al: The minimally conscious state: Definition and diagnostic criteria. *Neurology* 2002; 58: 349–353
14. Laureys S, Perrin F, Faymonville ME, et al: Cerebral processing in the minimally conscious state. *Neurology* 2004; 63:916–918
15. Coleman MR, Menon DR, Fryer TD, et al: Neurometabolic coupling in the vegetative and minimally conscious states: preliminary findings. *J Neurol Neurosurg Psychiatry* 2005; 76:432–434
16. Cairns HWB, Whitteridge D: Akinetic mutism with an epidermoid cyst of the 3rd ventricle. *Brain* 1941; 64:273–291
17. Ackermann H, Ziegler W: Akinetic mutism—A review of the literature. *Fortschr Neurol Psychiatr* 1995; 63:59–67
18. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness: American Congress of Rehabilitation Medicine. *Arch Phys Med Rehabil* 1995; 76:205–209
19. Cartlidge N: States related to or confused with coma. *J Neurol Neurosurg Psychiatry* 2001; 71(Suppl 1):i18–i19
20. Mesulam MM: Principles of Behavioral and Cognitive Neurology. Second Edition. New York, Oxford, Oxford University Press, 2000
21. American Psychiatric Association: Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Fourth Edition. Washington, DC, American Psychiatric Association, 2000
22. American Psychiatric Association: Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Fourth Edition. Washington, DC, American Psychiatric Association, 1994
23. Inouye SK, van Dyck CH, Alessi CA: Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990; 113:941–948
24. Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; 291:1753–1762
25. McNicoll L, Pisani MA, Zhang Y, et al: Delirium in the intensive care unit: Occurrence and clinical course in older patients. *J Am Geriatr Soc* 2003; 51:591–598
26. Burns A, Gallagley A, Byrne J: Delirium. *J Neurol Neurosurg Psychiatry* 2004; 75: 362–367
27. Smith E, Delargy M: Locked-in syndrome. *BMJ* 2005; 330:406–409
28. Vargas F, Hilbert G, Gruson D, et al: Fulminant Guillain-Barre syndrome mimicking cerebral death: Case report and literature review. *Intensive Care Med* 2000; 26: 623–627
29. Douglas NJ: The sleepy patient. *J Neurol Neurosurg Psychiatry* 2001; 71(Suppl 1): i3–i6
30. Taylor MA, Fink M: Catatonia in psychiatric classification: A home of its own. *Am J Psychiatry* 2003; 160:1233–1241
31. Rudolph U, Antkowiak B: Molecular and neuronal substrates for general anaesthetics. *Nat Rev Neurosci* 2004; 5:709–720
32. Wijdicks EFM: Neurologic Complications of Critical Illness. Contemporary Neurology Series 64. Second Edition. Oxford; New York, Oxford University Press, 2002
33. Kunze K: Metabolic encephalopathies. *J Neurol* 2002; 249:1150–1159
34. Cervical spine immobilization before admission to the hospital. *Neurosurgery* 2002; 50:S7–S17
35. Varon J, Marik PE: The diagnosis and management of hypertensive crises. *Chest* 2000; 118:214–227
36. Samuels MA: Neurally induced cardiac damage. Definition of the problem. *Neurol Clin* 1993; 11:273–292
37. Colice GL, Matthay MA, Bass E, et al: Neurogenic pulmonary edema. *Am Rev Respir Dis* 1984; 130:941–948
38. Chesnut RM, Marshall LF, Klauber MR, et al: The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; 34:216–222
39. Fearnside MR, Cook RJ, McDougall P, et al: The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical and CT variables. *Br J Neurosurg* 1993; 7:267–279
40. Zygun DA, Kortbeek JB, Fick GH, et al: Non-neurologic organ dysfunction in severe traumatic brain injury. *Crit Care Med* 2005; 33:654–660
41. Robertson CS, Valadka AB, Hannay HJ, et al: Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; 27:2086–2095
42. Sulte G, Elting JW, Langedijk M, et al: Admitting acute ischemic stroke patients to a stroke care monitoring unit versus a conventional stroke unit: A randomized pilot study. *Stroke* 2003; 34:101–104
43. Ziai WC: Coma and altered consciousness. In: Handbook of Neurocritical Care. Current Clinical Neurology. Bhardwaj A, Mirski MA, Ulatowski JA (Eds.) Totowa, NJ, Humana Press, 2004
44. The Brain Trauma Foundation: The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Glasgow Coma Scale Score. *J Neurotrauma* 2000; 17:563–571
45. Booth CM, Boone RH, Tomlinson G, et al: Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; 291:870–879
46. Winkler JV, Rosen P, Alfry EJ: Prehospital use of the Glasgow Coma Scale in severe head injury. *J Emerg Med* 1984; 2:1–6
47. Baxt WG, Moody P: The impact of advanced prehospital emergency care on the mortality of severely brain-injured patients. *J Trauma* 1987; 27:365–369
48. Massagli TL, Michaud LJ, Rivara FP: Association between injury indices and outcome after severe traumatic brain injury in children. *Arch Phys Med Rehabil* 1996; 77: 125–132
49. Servadei F, Nasi MT, Cremonini AM, et al: Importance of a reliable admission Glasgow Coma Scale score for determining the need for evacuation of posttraumatic subdural

hematomas: A prospective study of 65 patients. *J Trauma* 1998; 44:868–873
50. Sacco RL, VanGool R, Mohr JP, et al: Nontraumatic coma. Glasgow Coma Score and coma etiology as predictors of 2-week outcome. *Arch Neurol* 1990; 47:1181–1184
51. Rordorf GW, Koroshetz W, Efird JT, et al: Predictors of mortality in stroke patients admitted to an intensive care unit. *Crit Care Med* 2000; 28:1301–1305
52. Steiner T, Mendoza G, De Georgia M, et al: Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit. *Stroke* 1997; 28:711–715
53. Qureshi AI, Sung GY, Razumovsky AY, et al: Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. *Crit Care Med* 2000; 28:984–990
54. Tuhrim S, Dambrosia JM, Price TR, et al: Intracerebral hemorrhage: External validation and extension of a model for prediction of 30-day survival. *Ann Neurol* 1991; 29: 658–663
55. Tuhrim S, Dambrosia JM, Price TR, et al: Prediction of intracerebral hemorrhage survival. *Ann Neurol* 1988; 24:258–263
56. van de Beek D, de Gans DJ, Spanjaard L, et al: Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; 351:1849–1859
57. Bastos P, Sun PGX, Wagner DP, et al: Glasgow Coma Scale score in the evaluation of outcome in the intensive care unit: Findings from the Acute Physiology and Chronic Health Evaluation III study. *Crit Care Med* 1993; 21:1459–1465
58. Knaus W, Wagner DP, Draper EA, et al: The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619–1636
59. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13: 818–829
60. Knaus WA, Zimmerman JE, Wagner DP, et al: APACHE-acute physiology and chronic health evaluation: A physiologically based classification system. *Crit Care Med* 1981; 9:591–597
61. Le Gall JR, Loirat P, Alperovitch A, et al: A simplified acute physiology score for ICU patients. *Crit Care Med* 1984; 12:975–977
62. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
63. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
64. Marshall JC, Cook DJ, Christou NV, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; 23:1638–1652
65. Segatore M, Way C: The Glasgow Coma Scale: Time for change. *Heart Lung* 1992; 21:548–557
66. Sternbach GL: The Glasgow Coma Scale. *J Emerg Med* 2000; 19:67–71
67. Jagger J, Jane JA, Rimel R: The Glasgow Coma Scale: To sum or not to sum? *Lancet* 1983; 2:97
68. Shackford S, Wald SL, Ross SE, et al: The clinical utility of computed tomographic scanning and neurologic examination in the management of patients with minor head injuries. *J Trauma* 1992; 33:385–394
69. Borczuk P: Predictors of intracranial injury in patients with mild head trauma. *Ann Emerg Med* 1995; 25:731–736
70. Liu GT: Coma. *Neurosurg Clin N Am* 1999; 10:579–586, vii-viii
71. North JB, Jennett S: Abnormal breathing patterns associated with acute brain damage. *Arch Neurol* 1974; 31:338–344
72. Rafanan AL, Kakulavar P, Perl J II, et al: Head computed tomography in medical intensive care unit patients: clinical indications. *Crit Care Med* 2000; 28:1306–1309
73. Wilberger JE Jr, Deeb Z, Rothfus W: Magnetic resonance imaging in cases of severe head injury. *Neurosurgery* 1987; 20: 571–576
74. Yokota H, Kurokawa A, Otsuka T, et al: Significance of magnetic resonance imaging in acute head injury. *J Trauma* 1991; 31:351–357
75. Restrepo L, Wityk RJ, Grega MA, et al: Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. *Stroke* 2002; 33:2909–2915
76. Wityk RJ, Goldsborough MA, Hillis A, et al: Diffusion- and perfusion-weighted brain magnetic resonance imaging in patients with neurologic complications after cardiac surgery. *Arch Neurol* 2001; 58:571–576
77. Finelli PF, Uphoff DF: Magnetic resonance imaging abnormalities with septic encephalopathy. *J Neurol Neurosurg Psychiatry* 2004; 75:1189–1191
78. Hollinger P, Zurcher R, Schroth G, et al: Diffusion magnetic resonance imaging findings in cerebritis and brain abscesses in a patient with septic encephalopathy. *J Neurol* 2000; 247:232–234
79. Practice parameters: Lumbar puncture (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1993; 43: 625–627
80. Adelson-Mitty J, Fink MP, Lisbon A: The value of lumbar puncture in the evaluation of critically ill, non-immunosuppressed, surgical patients: A retrospective analysis of 70 cases. *Intensive Care Med* 1997; 23: 749–752
81. Metersky ML, Williams A, Rafanan AL: Retrospective analysis: Are fever and altered mental status indications for lumbar puncture in a hospitalized patient who has not undergone neurosurgery? *Clin Infect Dis* 1997; 25:285–288
82. Hasbun R, Abrahams J, Jekel J, et al: Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345:1727–1733
83. Towne AR, Waterhouse EJ, Boggs JG, et al: Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000; 54:340–345
84. Claassen J, Mayer SA, Kowalski RG, et al: Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology* 2004; 62:1743–1748
85. Varelas PN, Spanaki MV, Hacein-Bey L, et al: Emergent EEG: Indications and diagnostic yield. *Neurology* 2003; 61:702–704
86. Kaplan PW: The EEG in metabolic encephalopathy and coma. *J Clin Neurophysiol* 2004; 21:307–318
87. Kaplan PW, Genoud D, Ho TW, et al: Etiology, neurologic correlations, and prognosis in alpha coma. *Clin Neurophysiol* 1999; 110:205–213
88. Ch'ien LT, Boehm RM, Robinson H, et al: Characteristic early electroencephalographic changes in herpes simplex encephalitis. *Arch Neurol* 1977; 34:361–364
89. Smith JB, Westmoreland BF, Reagan TJ, et al: A distinctive clinical EEG profile in herpes simplex encephalitis. *Mayo Clin Proc* 1975; 50:469–474
90. Jennett B, Bond MR: Assessment of outcome after severe brain damage. *Lancet* 1975; 1:480–484
91. Jennett B, Snoek J, Bond MR, et al: Disability after severe head injury: Observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry* 1981; 44: 285–293
92. Kaye AH, Andrewes D: Glasgow Outcome Scale: Research scale or blunt instrument? *Lancet* 2000; 356:1540–1541
93. Emanuel LL, Barry MJ, Stoeckle JD, et al: Advance directives for medical care—A case for greater use. *N Engl J Med* 1991; 324: 889–895
94. Thompson BT, Cox PN, Antonelli M, et al: Challenges in end-of-life care in the ICU: Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003: Executive summary. *Crit Care Med* 2004; 32:1781–1784
95. Bates D: The prognosis of medical coma. *J Neurol Neurosurg Psychiatry* 2001; 71(Suppl 1):i20–i23
96. Medical aspects of the persistent vegetative state (2): The Multi-Society Task Force on PVS. *N Engl J Med* 1994; 330:1572–1579
97. Levy DE, Caronna JJ, Singer BH, et al: Predicting outcome from hypoxic-ischemic coma. *JAMA* 1985; 253:1420–1426
98. Madl C, Grimm G, Kramer L, et al: Early prediction of individual outcome after cardiopulmonary resuscitation. *Lancet* 1993; 341:855–858
99. Zandbergen EG, de Haan RJ, Stoutenbeek

CP, et al: Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet* 1998; 352:1808–1812
100. Attia J, Cook DJ: Prognosis in anoxic and traumatic coma. *Crit Care Clin* 1998; 14: 497–511
101. Young GB, Wang JT, Connolly JF: Prognostic determination in anoxic-ischemic and traumatic encephalopathies. *J Clin Neurophysiol* 2004; 21:379–390
102. Robinson LR, Micklesen PJ, Tirschwell DL, et al: Predictive value of somatosensory evoked potentials for awakening from coma. *Crit Care Med* 2003; 31:960–967
103. Gennarelli TA, Spielman GM, Langfitt TW, et al: Influence of the type of intracranial lesion on outcome from severe head injury. *J Neurosurg* 1982; 56:26–32
104. Teasdale E, Cardoso E, Galbraith S, et al: CT scan in severe diffuse head injury: Physiological and clinical correlations. *J Neurol Neurosurg Psychiatry* 1984; 47:600–603
105. Teasdale G, Teasdale E, Hadley D: Computed tomographic and magnetic resonance imaging classification of head injury. *J Neurotrauma* 1992; 9(Suppl 1):S249–S257
106. Hashimoto T, Nakamura N, Richard KE, et al: Primary brain stem lesions caused by closed head injuries. *Neurosurg Rev* 1993; 16:291–298
107. Ruff RM, Marshall LF, Crouch J, et al: Predictors of outcome following severe head trauma: Follow-up data from the Traumatic Coma Data Bank. *Brain Inj* 1993; 7:101–111
108. Eisenberg HM, Gary HE Jr, Aldrich EF, et al: Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. *J Neurosurg* 1990; 73:688–698
109. Adams HP Jr, Kassell NF, Torner JC: Usefulness of computed tomography in predicting outcome after aneurysmal subarachnoid hemorrhage: A preliminary report of the Cooperative Aneurysm Study. *Neurology* 1985; 35:1263–1267
110. Cusumano S, Paolin A, Di Paola F, et al: Assessing brain function in post-traumatic coma by means of bit-mapped SEPs, BAEPs, CT, SPET and clinical scores. Prognostic implications. *Electroencephalogr Clin Neurophysiol* 1992; 84:499–514
111. Levin HS, Williams D, Crofford MJ, et al: Relationship of depth of brain lesions to consciousness and outcome after closed head injury. *J Neurosurg* 1988; 69:861–866
112. Kampfl A, Schmutzhard E, Franz G, et al: Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet* 1998; 351: 1763–1767
113. Saunders DE, Clifton AG, Brown MM: Measurement of infarct size using MRI predicts prognosis in middle cerebral artery infarction. *Stroke* 1995; 26:2272–2276
114. Chalela JA, Wolf RL, Maldjian JA, et al: MRI identification of early white matter injury in anoxic-ischemic encephalopathy. *Neurology* 2001; 56:481–485
115. Fogel W, Krieger D, Veith M, et al: Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. *Crit Care Med* 1997; 25:1133–1138
116. Schoerkhuber W, Kittler H, Sterz F, et al: Time course of serum neuron-specific enolase. A predictor of neurological outcome in patients resuscitated from cardiac arrest. *Stroke* 1999; 30:1598–1603
117. Vos PE, Lamers KJ, Hendriks JC, et al: Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. *Neurology* 2004; 62:1303–1310
118. Rosen H, Sunnerhagen KS, Herlitz J, et al: Serum levels of the brain-derived proteins S-100 and NSE predict long-term outcome after cardiac arrest. *Resuscitation* 2001; 49: 183–191
119. Pelinka LE, Kroepfl A, Leixnering M, et al: GFAP versus S100B in serum after traumatic brain injury: Relationship to brain damage and outcome. *J Neurotrauma* 2004; 21:1553–1561
120. Karkela J, Pasanen M, Kaukinen S, et al: Evaluation of hypoxic brain injury with spinal fluid enzymes, lactate, and pyruvate. *Crit Care Med* 1992; 20:378–386
121. Zandbergen EG, de Haan RJ, Hijdra A: Systematic review of prediction of poor outcome in anoxic-ischaemic coma with biochemical markers of brain damage. *Intensive Care Med* 2001; 27:1661–1667
122. Becker KJ, Ulatowski JA: Disorders of consciousness. *In:* Current Therapy in Neurologic Disease. Current Therapy Series. Fifth Edition. Johnson RT, Griffin JW (Eds). St. Louis, MO, Mosby, 1997