**CME learning objectives**

- To review the basic pathophysiology of coma
- To understand the critical elements of neurologic examination of the comatose patient
- To recognize critical steps in treating the comatose patient

The authors disclose no financial interest in this article.

This is the first of two articles on critical care.

**Preview:** Coma is the most severe form of unresponsiveness, in which a patient is totally unaware of self and surroundings. With the patient so disengaged during examination, management can be particularly challenging. What steps should the primary care physician take to ensure the most appropriate care for a comatose patient? In this article, Drs Malik and Hess describe an evaluation plan, laboratory studies, and treatment options and discuss the prognosis associated with coma.


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Coma is defined as a sleeplike state with total absence of awareness of self and the environment, even after vigorous external stimulation. Coma is the most severe form of unresponsiveness, and by definition, comatose patients lie with their eyes closed.

To avoid confusion and to improve communication, it is helpful to describe the level of consciousness with terms such as "alert," "drowsy," "stuporous," or "comatose" and to avoid words like "lethargic" or "obtunded," which lack precise meanings. Because other conditions resemble coma, it is important to distinguish the cause of the problem as quickly as possible. Specifically, it is helpful to determine whether the patient is, in fact, in a coma or whether the patient's condition might more appropriately be called persistent vegetative state or locked-in syndrome (see box below).

**Causes of coma**

Coma results from one of two pathophysiologic mechanisms: a diffuse insult to both cerebral hemispheres or a focal lesion involving the ascending reticular activating system (ARAS) located in the upper pons, midbrain, and diencephalon. A lesion in one cerebral hemisphere will not produce coma; bihemispheric dysfunction is required. In most studies of comatose patients, the "big three" causes of coma are stroke, cranial trauma, and drug intoxication.
To assist in evaluation of coma, causes can be divided into two broad categories: structural or surgical (table 1) and metabolic or medical (table 2). Structural or surgical coma is usually associated with diffuse damage to both hemispheres from increased intracranial pressure or diffuse vascular damage. There may be a lesion in or displacement of the ARAS in the upper brainstem. In nontraumatic coma, there is a diffuse insult to both cerebral hemispheres from either an endogenous or exogenous toxin. This includes infectious causes (sepsis), drug overdose, and metabolic abnormalities, such as hyponatremia and hypernatremia.

<table>
<thead>
<tr>
<th>Table 1. Causes of structural or surgical coma</th>
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<tbody>
<tr>
<td><strong>Trauma</strong></td>
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<tr>
<td>Subdural injury</td>
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<tr>
<td>Epidural injury</td>
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<tr>
<td>Diffuse axonal injury</td>
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<tr>
<td>Brain contusions</td>
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<td>Penetrating head injury</td>
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<tr>
<td><strong>Intracranial hemorrhage</strong></td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>Intracerebral hemorrhage</td>
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<tr>
<td>Posterior fossa (pontine, cerebellar)</td>
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<tr>
<td>Supratentorial (basal ganglia, lobar)</td>
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<tr>
<td><strong>Ischemic stroke</strong></td>
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<tr>
<td>Large middle cerebral artery infarction with brain herniation</td>
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<tr>
<td>Brainstem stroke involving bilateral rostral pons or midbrain</td>
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<tr>
<td>&quot;Top of the basilar&quot; syndrome with bilateral infarction of thalami and rostral midbrain</td>
</tr>
<tr>
<td><strong>Diffuse microvascular abnormality</strong></td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Cerebral malaria</td>
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<tr>
<td><strong>Tumor</strong></td>
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<tr>
<td>Glioblastoma multiforme with herniation</td>
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<tr>
<td>Multiple metastatic lesions</td>
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<tr>
<td><strong>Other disorders</strong></td>
</tr>
<tr>
<td>Osmotic demyelination syndrome (central pontine myelinolysis)</td>
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</table>
Table 2. Causes of metabolic or medical coma

**Drug overdose**
Benzodiazepines, barbiturates, opioids, tricyclic agents

**Infectious disease**
Sepsis
Bacterial meningitis
Encephalitis (eg, herpes simplex, arboviral infection)

**Endocrine disorders**
Hypoglycemic reaction
Diabetic ketoacidosis
Hyperosmolar coma
Myxedema
Hyperthyroidism

**Metabolic abnormalities**
Hyponatremia
Hypernatremia
Uremia
Hepatic encephalopathy
Hypertensive encephalopathy
Hypomagnesemic pseudocoma

**Toxic reactions**
Carbon monoxide poisoning
Alcohol poisoning
Acetaminophen overdose
Ethylene glycol poisoning

**Medication side effects**
Reye's syndrome
Neuroleptic malignant syndrome
Central anticholinergic syndrome
Serotonin syndrome
Isoniazid intoxication

**Deficiency states**
Thiamine deficiency (Wernicke's encephalopathy)
Niacin deficiency (pellagra)

**Hypothermia**
Psychogenic coma
**Structural or surgical coma**

Patients with structural or surgical coma often have focal neurologic signs; dilated, unreactive pupils; or evidence of increased intracranial pressure. The two major causes are stroke and cranial trauma. Traumatic brain injuries include subdural, epidural, and subarachnoid hemorrhage and cerebral contusions. In addition, subarachnoid hemorrhage may occur in the absence of trauma, as in an aneurysmal bleed with or without focal signs.

In most cases of head trauma, loss of consciousness follows an obvious history of trauma. However, sometimes the history may not be so obvious. The patient may have had no or only brief loss of consciousness, followed by a lucid interval, followed by unconsciousness. This may signify a gradually expanding intracranial hematoma that needs immediate surgical evaluation and treatment. In any case of traumatic head injury followed by loss of consciousness, a computed tomographic (CT) scan is important to verify evidence of bleeding.

In some cases, the patient may not regain consciousness after head trauma, even though no evidence of structural damage is seen on imaging studies. Such cases may be due to diffuse axonal injury secondary to shear forces in head trauma. In diffuse axonal injury, there is widespread damage to axons throughout the brain but particularly in the dorsolateral pons and corpus callosum. However, an extensive search for other causes needs to be carried out before ascribing coma to diffuse axonal injury.

Strokes lead to coma by directly involving the ARAS (eg, pontine stroke) or by secondary edema and herniation leading to displacement of the ARAS. Cerebellar hemorrhages can produce coma rapidly by compressing the fourth ventricle, which results in obstructive hydrocephalus, or by directly compressing the brainstem. Herniation of the cerebellar tonsils can rapidly lead to death. Cerebellar hemorrhages and infarcts require urgent neurosurgical consultation and often decompressive craniectomy.

Supratentorial intracerebral hemorrhages most often occur in the basal ganglia (putamen) as a result of poorly controlled hypertension. These hemorrhages produce coma by mass effect and herniation. Surgical interventions are controversial in this type of hemorrhage.

Large infarctions of the middle cerebral artery can become edematous, leading to malignant middle cerebral artery occlusions and brain herniation (1). The edema usually peaks about 2 to 5 days postinfarction, and patients often first appear to be in stable condition and then deteriorate. They need to be closely monitored in an intensive care unit. Although treatment options currently are limited, a study funded by the National Institutes of Health is examining whether hemicraniectomy and durotomy improve functional outcome (2).

**Metabolic or medical coma**

Patients with this type of coma generally have reactive pupils, an absence of focal neurologic signs, and no evidence of increased intracranial pressure. There are some exceptions to these general rules. For example, patients with acute hepatic...
encephalopathy and hyperammonemia often have increased intracranial pressure, which can lead to death. Ayus and associates (3) have reported on increased intracranial pressure that has led to herniation and death in menstruant women with iatrogenic acute hyponatremia. Patients with hyperosmolar states (nonketotic hyperglycemia) may present with focal neurologic signs, especially focal seizures, as may hypoglycemic patients.

**Neurologic evaluation**

The most important element in the evaluation of the comatose patient is obtaining a history from observers on the scene of the triggering event, from family members, and from emergency medical technicians who responded to the call for help. The coma examination then can be performed rapidly and can guide diagnostic testing and therapeutic measures. The examination has four important components:

- Respiratory patterns
- Pupillary responses
- Eye movements
- Motor responses

**Respiratory patterns**

Breathing patterns can provide helpful clues to the cause of coma but are often ignored because of widespread use of mechanical ventilation. Cheyne-Stokes breathing is a respiratory pattern that oscillates between hypoventilation and hyperventilation. It usually results from bilateral or diencephalic insult but may occur as a result of damage anywhere between the forebrain and the pons.

Stable Cheyne-Stokes breathing usually portends a good prognosis. However, in a patient with a unilateral mass lesion, onset of Cheyne-Stokes breathing may signify impending herniation. Short-cycle periodic breathing is similar to Cheyne-Stokes but has a faster cycle with one or two waxing breaths, followed by three or four rapid breaths, followed by one or two waning breaths. It is the result of increased intracranial pressure, expanding posterior fossa lesions, or a lower pontine lesion (4).

Central neurogenic hyperventilation usually results from lesions of the central tegmentum of the pons, ventral to the aqueduct or the fourth ventricle. Patients breathe 40 to 70 times per minute. It is important to distinguish central neurogenic hyperventilation from pulmonary disorders. In general, central nervous system lesions cannot be blamed for hyperpnea if $P_{O_2}$ is less than 80 mm Hg or $P_{CO_2}$ is greater than 40 mm Hg.

Apneustic breathing consists of a prolonged inspiratory gasp with a pause at end of inspiration, followed by expiration. Apneustic breathing is caused by lesions of the dorsolateral lower half of the pons (4). Cluster breathing, which results from high medullary damage, involves periodic breathing with irregular frequency and amplitude, along with variable pauses between clusters of breaths. Ataxic breathing is irregular in both rate and rhythm, is caused by medullary lesions, and usually is a preterminal pattern.
**Pupillary responses**
Examination of the pupils is the most important part of the coma examination (figure 1). Pupils reactive to light almost always indicate metabolic or medical coma. Pupils that are bilaterally reactive to light and symmetrical in size usually point to a metabolic cause and make brain herniation or a neurosurgical emergency unlikely. However, in a patient who has cerebellar hemorrhage or infarction, pupils may be equal and reactive initially. Lesions below the pons and above the thalamus usually do not cause pupillary abnormalities, except for Horner's syndrome associated with medullary or cervical spinal cord lesions.

An unreactive, unequal, dilated pupil may be a sign of herniation of the uncus (part of the temporal lobe) and represents a neurosurgical emergency. Pressure on the third nerve after its exit from the midbrain results in failure of parasympathetic innervation to the eye. This pressure on the third nerve can arise from a herniating uncus or an expanding posterior communicating artery aneurysm.

Pontine lesions disrupt sympathetic pathways and cause "pinpoint pupils," which are reactive to light but may be seen only through a magnifying glass. A patient presenting in coma with pinpoint pupils should be suspected of having a pontine hemorrhage or large brainstem or pontine infarction.

**Eye movements**
Eye movement evaluation consists of three steps: observing the resting position of the eyes, evaluating spontaneous movements, and investigating reflex eye movements. In the first step, the resting position of the eyes in an unresponsive patient often involves dysconjugate gaze in the horizontal plane. Vertical displacement of the eyes is known as "skew" deviation and usually indicates a brainstem lesion.
The second step in examining the eyes is to observe any spontaneous eye movements. Roving, slow, conjugate, lateral to-and-fro movements are usually seen in metabolic encephalopathies or bilateral lesions above the brainstem. Ocular bobbing consists of a rapid downward jerk of both eyes, followed by slow return to midposition (5). Paralysis of reflex and spontaneous lateral eye movements tends to be associated with acute pontine lesions. Inverse ocular bobbing or ocular dipping, which consists of a slow downward phase followed by a rapid upward phase and preserved reflex eye movements, is often associated with diffuse cerebral damage.

The third step in the ocular examination is to determine if reflex eye movements are present. This involves the oculocephalic reflex, or what is commonly referred to as "doll's eyes." When the head is rotated laterally in a patient with intact brainstem function, the eyes should move in a direction opposite to the movement of the head. Absence of the response may indicate brainstem dysfunction.

The oculocephalic reflex should never be checked until the stability of the neck is ensured by lateral cervical spine radiographic studies. If there is any doubt about neck stability, evaluation of caloric response can be substituted for head rotation. For caloric testing, the integrity of the tympanic membrane is first ascertained, and then 40 to 60 mL of ice water is used to irrigate the ear. If the brainstem is intact, the eyes deviate to the side of the cold water. The fast corrective component of eye movement is away from the stimulated ear. The latter movement is dependent upon cortical function and is absent in a comatose patient; only the slow phase toward the stimulated ear should be present. Absence of response to caloric testing may suggest brainstem dysfunction.

Motor responses

It is important to observe the comatose patient for any spontaneous motor movements, which are always good prognostic signs. If the patient spontaneously moves only one side, a hemispheric or brainstem lesion is probably present contralateral to the side not moving. If there are no spontaneous movements, a noxious stimulus, such as nail bed or supraorbital pressure, should be applied (figure 2).

Decorticate posturing (flexion at the elbow and wrist bilaterally, with shoulder adduction and extension of the legs) suggests a lesion above the brainstem, specifically above the red nucleus (figure 3a). Decerebrate posturing (internal rotation and adduction of the shoulder with extension at elbows, wrists, and legs) is usually associated with a bilateral midbrain or pontine lesion (figure 3b). This lesion is classically at the level of the red nucleus on the midbrain. Rarely, metabolic encephalopathies, such as hypoglycemia, may produce a similar picture. In general, decerebrate posturing has a worse prognosis than decorticate posturing.

Myoclonus consists of nonrhythmic jerking movements in single or multiple muscle groups and usually is associated with anoxic injuries (cortical reflex myoclonus) or metabolic encephalopathies, such as hepatic encephalopathy. Rhythmic myoclonus suggests brainstem injury.
Laboratory studies and treatment

Every patient with coma of unknown cause should undergo an immediate fingerstick test to measure blood glucose level, followed by administration of 100 mg of intravenous thiamine and dextrose, if indicated. If there is suspicion of a narcotic overdose, naloxone hydrochloride (Narcan), 0.4 to 4 mg, should be given intravenously. Higher doses may be needed in the case of an overdose of synthetic opioids (eg, fentanyl [Sublimaze], propoxyphene [Darvon]). When benzodiazepine overdose is suspected, flumazenil (Romazicon), 0.3 to 0.5 mg (maximum, 2 mg), should be given intravenously, provided there is no history of seizures.

Laboratory evaluation should include a metabolic panel for evaluating electrolytes, liver enzyme levels, complete blood cell count with differential, and prothrombin time and partial thromboplastin time for assessing coagulation abnormalities. If there is evidence of respiratory compromise, an arterial blood gas evaluation should be obtained. A history of heart disease or trauma or neuroleptic use suggests a need to measure creatine kinase. If there is a history or suspicion of drug or alcohol abuse, a urine drug screen and alcohol level should be obtained.

If no cause of coma is evident, an arterial ammonia level should be obtained, even if jaundice and liver enzyme level abnormalities are absent. These tests may be followed by thyroid studies or evaluation of serum cortisol levels if the patient's history suggests these studies might be helpful.

CT scans of the head should be ordered for any patient with a history of head trauma, sudden onset of severe headache, focal neurologic deficit, or episodes of vomiting before onset of coma. Lumbar puncture and cerebrospinal fluid studies should be performed in any patient with a history of fever, stiff neck, seizure, or sudden severe headache. However, the CT scans should be performed first in any comatose patient, especially when focal neurologic signs are present.

A patient with a history of seizures or in whom there is eyelid blinking or unexplained nystagmus should undergo an electroencephalographic evaluation to determine if nonconvulsive status epilepticus is the cause of the coma. A recent study (6) showed that nonconvulsive status epilepticus occurred in 8% of comatose patients and suggested that this seizure disorder may be an underrecognized cause of coma.

Diffuse slowing on the electroencephalogram may indicate a metabolic encephalopathy. Triphasic waves may suggest hepatic encephalopathy, whereas periodic lateralized epileptiform discharges may suggest herpes simplex encephalitis.

With metabolic or medical coma, correction of the metabolic derangement and treatment of the underlying cause are essential, along with supportive care. A neurosurgeon should be consulted if there is evidence of an unreactive, dilated pupil or if the CT scan shows a large hemorrhage. In a patient who is rapidly deteriorating because of brain herniation, immediate treatment of increased intracranial pressure should include hyperventilation to
a $\text{P}_{\text{CO}_2}$ of 25 mm Hg and administration of mannitol (Osmitrol) (1 g/kg). The indications for intracranial pressure monitoring remain controversial; its use is best established in cases of traumatic brain injury and in states of hyperammonemia (eg, Reye's syndrome).

**Prognostic factors**

Metabolic causes of coma carry the best prognosis, whereas coma associated with structural damage, such as cerebrovascular disease or subarachnoid hemorrhage, tends to have the poorest prognosis. Hypoxic-ischemic injury has a poor prognosis also. As a general rule, patients with a nontraumatic cause of coma usually do not regain consciousness if they have been comatose or in a vegetative state for more than a month.

Levy and colleagues (7) reported outcomes for a series of 210 patients who experienced coma from cerebral hypoxia-ischemia. In this type of coma, neurologic findings are predictive of outcome. At the time of initial evaluation (6 hours or more after onset of coma), absence of pupillary reflexes was associated with no recovery of independent function. No patient who lacked corneal reflexes on or after the first day regained consciousness. After 3 days, absent or posturing responses were incompatible with eventual independence. The most favorable sign was incoherent speech (moaning) at these early time points. On day 1, the following signs were associated with a 50% chance of independence: confused or inappropriate speech, orienting spontaneous eye movements, normal oculocephalic or oculovestibular responses, and obedience to commands.

In patients with traumatic coma, the length of coma does not necessarily imply a poor prognosis. The outcome from head injury depends primarily on the level of consciousness at the outset of injury and on the age of the patient.

Jennett and colleagues (8) studied 1,000 patients in coma longer than 6 hours after severe head trauma. Among these patients, 49% died, 3% remained vegetative, 10% survived with severe disability, 17% survived with moderate disability, and 22% had good recovery. Depth of coma evaluated by the Glasgow Coma Scale (table 3), pupillary response, eye movements, and motor response in the first week after injury, as well as age, were found to be the most reliable predictors of outcome 6 months later. No measure is yet available for accurately determining an individual patient's prognosis, but the above-mentioned parameters may serve as useful guidelines.
### Table 3. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye opening (E)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
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</table>

**Best motor response (M)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Obeys</td>
<td>6</td>
</tr>
<tr>
<td>Localizes</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion posturing</td>
<td>3</td>
</tr>
<tr>
<td>Extension posturing</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
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</table>

**Verbal response (V)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
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<tbody>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused conversation</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

Total score = \( E + M + V \)

Range of possible scores = 3-15

A score of 13 to 15 indicates mild coma. A score between 9 and 12 points to moderate coma, and a score of 8 or less indicates severe coma.

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**Summary**

Coma is defined as a sleeplike state in which the patient is unresponsive to self and the environment. Coma should be distinguished from the persistent vegetative state and locked-in syndrome. It is important to obtain a carefully taken history from eyewitnesses and to perform a rapid neurologic examination focusing on pupillary responses, eye movements, and motor responses. Pupils reactive to light usually indicate metabolic or medical coma; cerebellar infarction or hemorrhage is a notable exception. A pupil unreactive to light often points to a structural brain lesion and the need for urgent neurosurgical consultation. The prognosis for coma depends on the cause.
Conditions that resemble coma

In the evaluation of a comatose or semicomatose patient, it is important to consider many possible causes for lack of responsiveness. Among these are the following:

Persistent vegetative state

This is a permanent condition that emerges after severe brain injury. It is associated with normal sleep-wake cycles and eyes that open to verbal stimuli. However, the patient has no cognitive function. The patient cannot localize pain or follow verbal commands, but blood pressure and respiration are maintained. Other terms for this state include so-called coma vigil, apallic syndrome, cerebral death, neocortical death, and total dementia. The most common cause is anoxic-ischemic injury.

Locked-in syndrome

Patients in this state are conscious of their environment but unable to move any extremities, talk, or have horizontal eye movements (de-efferented state). The only communication may be through vertical eye movements and blinking. The lesion is in the brainstem and involves the motor pathway, the efferent abducent nerve fibers, and the corticobulbar fibers. Common causes include pontine infarct from basilar artery thrombosis, pontine hemorrhage, and central pontine myelinolysis. At times, patients with severe Guillain-Barré syndrome can appear to be "locked in."

References

1. Frank JI. Large hemispheric infarction, deterioration, and intracranial pressure. Neurology 1995;45(7):1286-90