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Coma and Brain Death

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ABSTRACT

PURPOSE OF REVIEW: This article discusses the diagnostic and therapeutic approach to patients who are comatose and reviews the current knowledge on prognosis from various causes of coma. This article also provides an overview of the principles for determination of brain death as well as advice on how to avoid common pitfalls.

RECENT FINDINGS: Technologic advances have refined our understanding of the physiology of consciousness and the spectrum of disorders of consciousness; they also promise to improve our prognostic accuracy. Yet the clinical principles for the evaluation and treatment of coma remain unaltered. The clinical standards for determination of death by neurologic criteria (ie, brain death) are also well established, although variabilities in local protocols and legal requirements remain a problem to be resolved.

SUMMARY: Effective evaluation of coma demands a systematic approach relying on clinical information to ensure rational use of laboratory and imaging tests. When the cause of coma is deemed irreversible in the setting of a catastrophic brain injury and no clinical evidence exists for brain and brainstem function, patients should be evaluated for the possibility of brain death by following the clinical criteria specified in the American Academy of Neurology guidelines.

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INTRODUCTION

Consciousness is the cerebral function that defines our identity, yet the definition of this primordial function is elusive, and the complex mechanisms underlying its existence and preservation are just beginning to be unraveled. More is known about loss of consciousness, which results in the state known as coma. However, clinical evaluation of consciousness is far from straightforward. For example, growing understanding of the spectrum of chronic disorders of consciousness demonstrates that minimally preserved consciousness may not be apparent even to the examiner at the bedside.[1]

Catastrophic brain injury can result in irreversible coma with cessation of all brain (and brainstem) function. When this occurs, patients can be legally declared dead by neurologic criteria (ie, brain death) and become eligible as organ donors. Needless to say, determination of brain death is an enormous responsibility. It demands a conscientious and detailed evaluation, which has been carefully described in guidelines published by the American Academy of Neurology (AAN).[2]

Coma and brain death are two core topics in any neurologic training curriculum, and having in-depth knowledge of these clinical scenarios is essential

for every neurologist practicing in a hospital setting. Nonetheless, misinformation and misunderstandings are not uncommon in evaluation and prognosis of coma and determination of brain death. This article provides an updated, practical, and systematic approach to clarify key concepts and highlights potential pitfalls that may result in serious medical errors.

KEY POINTS

- Coma is a state of unresponsiveness in which the patient is not awake and cannot interact with the environment, even after vigorous stimulation.
- Bilateral diffuse alterations in cortical function or severe diencephalic or brainstem dysfunction can produce coma.

COMA

Coma is commonly defined as a state of unresponsiveness in which the patient is not awake and cannot interact with the environment, even after vigorous alerting stimulation. It lies at one end of a continuum of depression in the level of consciousness, a spectrum that also comprises less severe states of decreased responsiveness such as drowsiness (awakening to verbal stimulation) and stupor (interaction with the environment elicited by alerting noxious stimulation). These terms can be helpful for communication, but specifically describing the patient's responses to various forms of stimulation is often clearer.

It is important to remember that consciousness is best conceptualized as having two domains: level and content. Level of consciousness refers to the degree of arousal (ie, is the patient fully awake or does he or she require stimulation to awaken and respond?), while content of consciousness refers to the degree of awareness (ie, is the patient coherent or is he or she confused, inattentive, or delusional?). Both domains should be evaluated, except when the severity of depression in the level of consciousness precludes evaluation of its content.

Pathophysiologic Mechanisms

The anatomic and physiologic underpinnings of human consciousness are incompletely understood, yet we know that bilateral diffuse alterations in cortical function or severe alterations in diencephalic or brainstem function can result in coma.

It is common to distinguish between coma caused by structural brain damage and coma caused by diffuse cerebral dysfunction.[3] This distinction, while pragmatically useful, is sometimes imprecise. Patients with a brain tumor can become comatose from mass effect and tissue shift or from seizures. After prolonged refractory status epilepticus, patients may remain comatose because of cortical injury even after resolution of the seizures that were responsible for the initial loss of responsiveness. Nonetheless, it is always useful to try to localize the cause of coma when possible.

A basic anatomic classification of coma is presented in TABLE 6-1.

Anatomic Classification of Coma TABLE 6-1

- Hemispheric brain lesion with tissue shift and herniation
- Diffuse bilateral hemispheric damage
- Bilateral diencephalic lesions
- Cerebellar lesion causing brainstem compression
- Intrinsic brainstem lesion
- Hydrocephalus

Supratentorial lesions typically cause coma by mass effect, tissue shift, and herniation. Lateral tissue displacement causes subfalcine herniation, while vertical tissue shift produces transtentorial (uncal) and eventually transforaminal herniation. However, the gradient induced by the mass effect is not unidirectional, and, in most cases, lateral and vertical displacements are combined.

Another way to categorize coma is by the type of condition responsible for its occurrence (TABLE 6-2).[3,4] Coma can be the end result of many forms of severe brain dysfunction, including cerebrovascular events, trauma, anoxia, infections, noninfectious inflammation, hydrocephalus, seizures, intoxications, metabolic disturbances, sepsis, and extreme alterations in body temperature. Notably, several causes can be combined. Common combinations include anoxia and seizures; trauma and anoxia, sepsis, drug effects, or metabolic disturbances; and intracranial hemorrhage and hydrocephalus. In these cases, the relative contribution of each

TABLE 6-2 **Common Causes of Coma**

Global Anoxia/Ischemia

Cerebrovascular Disease

- Massive hemispheric infarction or hematoma
- Brainstem ischemic stroke from basilar artery occlusion
- Brainstem hemorrhage
- Cerebellar infarction or hematoma with mass effect
- Poor-grade aneurysmal subarachnoid hemorrhage
- Dural venous sinus thrombosis

Trauma

- Diffuse axonal injury
- Brain edema and intracranial hypertension
- Epidural or subdural hematoma
- Hemorrhagic brain contusions with mass effect
- Fat embolism

Infection

- Acute bacterial meningitis
- Acute viral encephalitis
- Fungal or mycobacterial meningoencephalitis
- Brain abscesses
- Empyema

Inflammatory

- Autoimmune encephalitis
- Posterior reversible encephalopathy syndrome (PRES)
- Vasculitis
- Acute disseminated demyelination

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cause may not be initially apparent, but recognition of every possible cause and treatment of those that are treatable are crucial to optimize the chances of recovery.

Evaluation

Although many practitioners rush to order tests when confronted with a patient who is comatose, the main clues to the etiology of the coma can often be obtained by a focused history and a skillful physical examination.[4] Furthermore, because the causes of coma are so many and so varied, a shotgun approach to testing can generate more confusion by offering abnormal results of unclear relevance. Thus, testing, with the exception of capillary glucose, should be guided by the information provided by the history and the examination.

History taking should focus on obtaining the details of the presentation, pertinent past medical history, and recent exposures. A crucial question is

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Tumor

- Large hemispheric tumors with edema and mass effect
- Brainstem tumors
- Cerebellar tumors with mass effect
- Infiltrative tumors
- Pituitary apoplexy

Acute Hydrocephalus

Seizures

Toxins

- Prescription drug overdose
- Recreational drug overdose
- Drug interactions
- Poisoning

Metabolic and Endocrine Abnormalities

- Hyponatremia
- Hypercalcemia
- Acidosis
- Renal failure and uremia
- Hepatic failure and hyperammonemia
- Myxedema
- Adrenal insufficiency

Hypothermia

whether the onset was witnessed. Acuteness of onset, preceding symptoms, abnormal movements, urinary incontinence, and signs that breathing may have been impaired are also essential pieces of information. Diabetes mellitus, obstructive pulmonary disease, epilepsy, previous brain injury, brain tumor, recent neurosurgery, immunosuppression, and conditions requiring anticoagulation are among the most relevant comorbid conditions that should be specifically considered. Clues to the possibility of intoxication with prescription or recreational drugs should be explored.[4]

The physical examination should begin by ensuring the adequacy of the airway, breathing, and circulation. Fever can denote underlying sepsis or central nervous system (CNS) infection. Hypothermia, when severe, can be solely responsible for the coma. Dyspnea and cyanosis may indicate that the altered consciousness can be reversed by correction of hypercapnia. Shock is a common cause of altered mentation and even coma and demands its own evaluation. The

TABLE 6-3

Glasgow Coma Scale[a]

Response	Score[b]
Eye response (E)	
No eye opening	1
Eye opening to pain	2
Eye opening to verbal command	3
Spontaneous eye opening	4
Verbal response (V)[c]	
No verbal response	1
Incomprehensible sounds	2
Inappropriate words	3
Confused	4
Oriented	5
Motor response (M)	
No motor response	1
Stereotyped extension to pain	2
Stereotyped flexion to pain	3
Withdrawal from pain	4
Localizes pain	5
Follows commands	6

[a] Data from Teasdale G, Jennett B, Lancet.[6]

[b] Maximal sum score is 15 points. Coma is usually defined as a score of 8 points or less.

[c] By convention, when the patient is intubated, the verbal response score is reported as 1 and T (endotracheal tube or intubated) and is added to qualify the sum score. Alternatively, the verbal response score can be estimated from the other two scores, as is shown in TABLE 6-4.[7,8]

general examination should include inspection of the skin; for example, a petechial rash can alert the clinician to the possibility of fulminant meningitis.

The neurologic examination of the patient who is comatose, although deceivingly simple and rarely diagnostic by itself, can offer extremely useful information.[4] Attention should be paid to the degree of unresponsiveness, brainstem reflexes, position of the eyes, muscle tone, focal or lateralizing signs, adventitious movements of the eyes and limbs, and meningeal signs. Differentiating the very common abnormal movements associated with toxic and metabolic causes from motor manifestations of seizures can be challenging, especially for less seasoned clinicians. While the former are typically arrhythmic myoclonic jerks and asterixis and the latter are characteristically rhythmic and usually respect a more consistent pattern, EEG is indicated when uncertainty persists after careful observation.

Using a validated scale to categorize the degree of coma is useful for triaging, subsequent monitoring through serial examinations, and prognosis. The Glasgow Coma Scale (GCS) was originally designed for acute evaluation of alterations of consciousness from traumatic brain injury in the field[5] but was later applied to all other causes of coma (TABLE 6-3).[6] The GCS is widely used, but it has noticeable shortcomings: (1) it loses one of its three components (ie, the verbal component) when the patient is intubated; (2) it does not incorporate an evaluation of the brainstem reflexes or the breathing pattern, which are crucial elements in the assessment of any patient who is comatose; and (3) it is skewed toward the motor response, particularly in patients who are intubated, for whom it accounts for 6 of 10 possible points, although it may be possible to estimate the verbal component based on motor and eye scores to overcome this limitation in patients who are comatose and intubated (TABLE 6-3 and TABLE 6-4).[7,8] The Full Outline of UnResponsiveness (FOUR) score, developed by Wijdicks and colleagues,[9] addresses these deficiencies of the GCS and has been shown to be comparable or superior to the GCS for prognostication across various types of severe brain injury (FIGURE 6-1 and TABLE 6-5).[10–12]

Having a checklist in mind when assessing a patient who is comatose is recommended (TABLE 6-6). Essentially, all patients who are comatose will require some blood tests to exclude major primary or secondary metabolic abnormalities, but beyond that, the laboratory investigations should be individualized. A toxicologic screen is reasonable when the cause of coma is uncertain. Blood urea nitrogen and serum ammonia should be measured in most cases.

Brain imaging is often, but not always, necessary. It becomes indispensable after head trauma, when the physical examination shows focal deficits or asymmetric motor responses, and when meningitis is suspected to ensure that lumbar puncture can be performed safely. A head CT is often obtained first and has good sensitivity to detect acute intracranial hemorrhage, hydrocephalus, and brain tissue shift from a mass (FIGURE 6-2). Contrast administration is useful when infection or tumor is possible.

Brain MRI is more sensitive for the recognition of most other causes of coma and also helps clarify causes when the CT is abnormal but the diagnosis remains indeterminate. Examples of coma etiologies that can be reliably diagnosed with MRI include herpes simplex virus type 1 encephalitis, brainstem infarction, and posterior reversible encephalopathy syndrome (PRES), the latter in most but not all cases (FIGURE 6-3). Brain MRI can also show cortical and basal ganglia damage after global brain anoxia-ischemia, diffuse axonal injury

KEY POINTS

- Focused history and physical examination very often provide clues to the etiology of coma.
- Coma scales are useful but should not replace a more complete neurologic examination.
- The differential diagnosis and diagnostic testing should be guided by the history, physical examination, and location of the patient (out of hospital, in the emergency department, on a hospital floor, or in the intensive care unit).
- CT is a reasonable and practical first imaging study when structural damage is suspected, but MRI may be more useful for various causes of coma.

after trauma, small infarctions from an embolic shower (including cerebral fat embolism), venous infarctions in cases of dural or deep venous sinus thrombosis, cortical injury after prolonged status epilepticus, pontine and supratentorial demyelination after rapid osmotic changes, and signs of infiltrative brain tumor that might not be appreciable on head CT. However, not every case of coma from a structural brain injury will have an abnormal MRI. For example, some forms of viral encephalitis (such as those caused by arboviruses), a minority of cases with hypertensive encephalopathy, and some cases of persistent coma after cardiopulmonary resuscitation may have normal appearance on brain MRI.

Noninvasive vessel imaging should be guided by clinical suspicion of a particular diagnosis, most notably acute basilar artery occlusion or dural venous sinus thrombosis. Ordering CT angiography (CTA) or magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) is not necessary in most cases of coma, and the author has found these studies to be grossly overused for this indication. Catheter angiography is very rarely indicated.

A lumbar puncture can be diagnostic in patients with CNS infection and provides helpful clues in some other instances, such as in autoimmune encephalitis. Low glucose levels can be seen after severe hypoglycemia (it takes longer for the glucose level to normalize in the CSF than in blood) and with fungal infections. High protein is quite common and nonspecific; it can be seen with inflammation, infection, venous thrombosis, and seizures, among others.

The EEG is always abnormal in patients who are comatose but is far less commonly useful for reaching a specific diagnosis or assisting in management. It is definitely indicated in patients who fail to awaken after a prolonged clinical seizure or multiple clinical seizures and when ongoing subtle clinical manifestations of seizures are suspected. In fact, when seizures are strongly suspected, it is advisable to extend the period of monitoring for at least a few hours, if possible, before concluding that the coma is not being perpetuated by

TABLE 6-4 **Glasgow Coma Scale Predictive Verbal Score**[a,b]

Glasgow Coma Scale Motor Score	Glasgow Coma Scale Eye Score			
	1	2	3	4
1	1	1	1	2
2	1	1	1	1
3	1	1	1	2
4	2	1	2	2
5	3	2	3	3
6	4	4	4	5

[a] Reprinted with permission from Rutledge R, et al, J Trauma.[7] © 1996 Williams & Wilkins.

[b] This table can be used in patients who are intubated to predict what the verbal score would be if the patient were not intubated. It relies on the combination of the eye and motor scores of the Glasgow Coma Scale to estimate the verbal score. For instance, a patient who is intubated with a motor score of 4 and an eye score of 3 would be predicted to have a verbal score of 2.

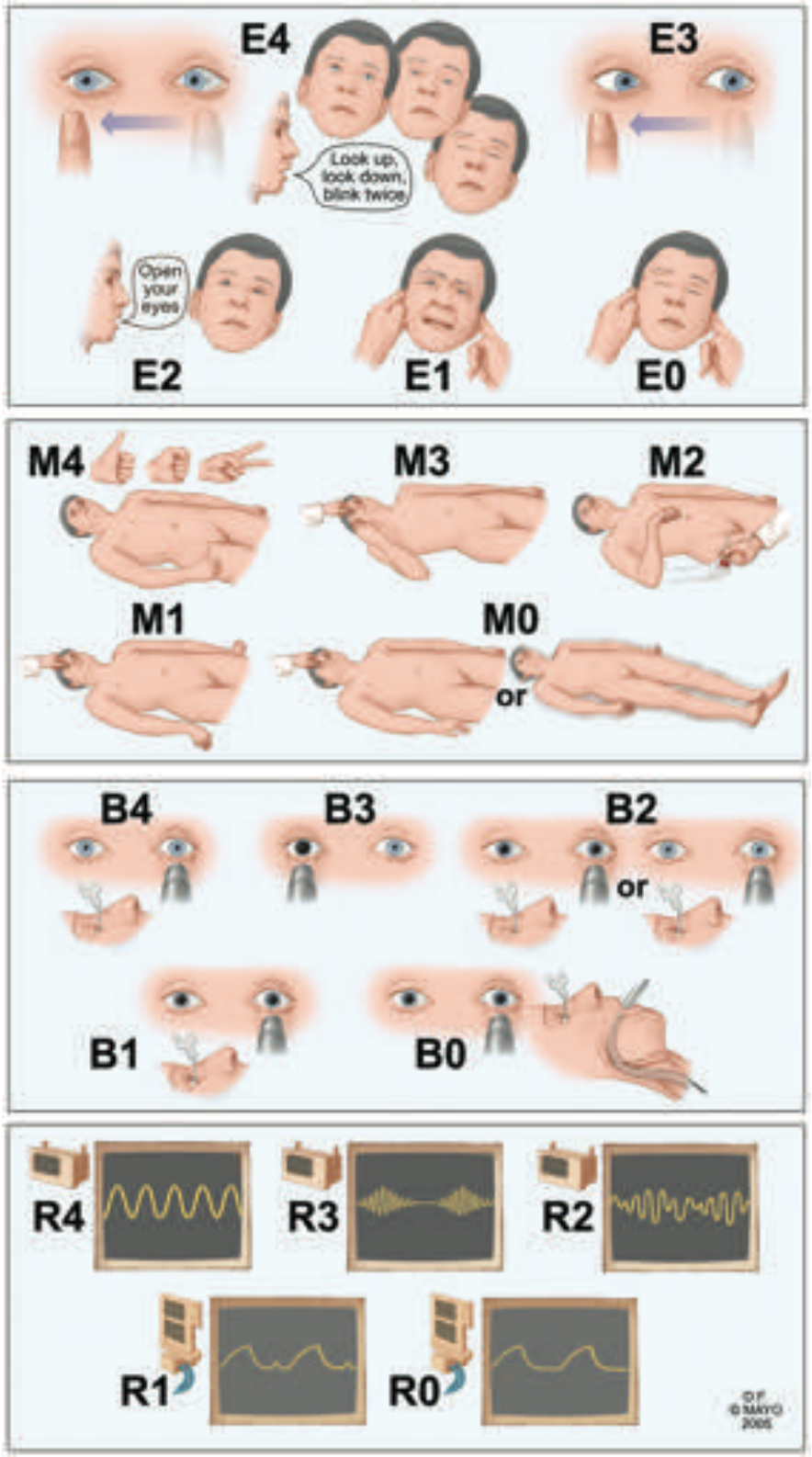

FIGURE 6-1

Full Outline of UnResponsiveness (FOUR) score. Additional explanations on scoring are provided in TABLE 6-5.

E = eye response; M = motor response; B = brainstem reflexes; R = respiration.

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KEY POINT

- **The value of EEG for the evaluation of patients who are comatose without clinical seizures remains to be established.**

intermittent seizures. Conversely, the value of EEG in patients who are comatose in general is much less clear. Some advocate EEG monitoring for all patients in coma, and some observational studies have reported a relatively high yield of epileptiform abnormalities by following this approach.[13] However, we are just learning about the significance of these abnormalities in the ictal-interictal continuum, and improvement in clinical outcomes from treating epileptiform abnormalities with antiseizure medications in patients who are comatose has not been proven. These abnormalities may just be manifestations of the brain

TABLE 6-5

The Full Outline of UnResponsiveness (FOUR) Score[a]

Score	Response
Eye response	
4	Eyelids open or opened, tracking, or blinking to command
3	Eyelids open but not tracking
2	Eyelids closed but open to loud voice
1	Eyelids closed but open to pain
0	Eyelids remain closed with pain
Motor response	
4	Thumbs-up, fist, or peace sign
3	Localizing to pain
2	Flexion response to pain
1	Extension response to pain
0	No response to pain or generalized myoclonus status
Brainstem reflexes	
4	Pupil and corneal reflexes present
3	One pupil wide and fixed
2	Pupil or corneal reflexes absent
1	Pupil and corneal reflexes absent
0	Absent pupil, corneal, and cough reflex
Respiration	
4	Not intubated, regular breathing pattern
3	Not intubated, Cheyne-Stokes breathing pattern
2	Not intubated, irregular breathing
1	Breathes above ventilatory rate
0	Breathes at ventilator rate or apnea

[a] Modified with permission from Wijdicks EF, et al, Ann Neurol.[9] © 2005 John Wiley and Sons.

Checklist for the Evaluation of Acute Coma

TABLE 6-6

History

- Sudden onset? Witnessed onset?
- Previous level of function
- Comorbid conditions
- Medications and toxic exposures
- Previous episodes of altered consciousness?
- Location (out of hospital, hospital floor, intensive care unit)

Physical Examination

- Vital signs
- Brainstem reflexes
- Funduscopy
- Motor responses to pain
- Lateralizing or other focal findings?
- Meningeal signs?
- Adventitious movements?

Blood (and Urine) Tests

- Glucose, electrolytes, blood urea nitrogen/creatinine, complete blood cell count
- Consider pH, $PaCO_2$, liver enzymes, ammonia, ethanol, toxicologic screen (urine and sometimes serum), levels of prescribed drugs, thyroid-stimulating hormone (TSH), cortisol
- Infectious workup (when pertinent)
- Autoimmune encephalitis panel (when pertinent)

Brain Imaging?

- Brain parenchyma (CT versus MRI)
- Brain vessels (arteries, veins)

Lumbar Puncture?

- Glucose, protein, nucleated cells
- Infectious workup (when pertinent)
- Autoimmune encephalitis panel (when pertinent)

EEG?

- Spot versus continuous

CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging; $PaCO_2$ = partial pressure of carbon dioxide, arterial.

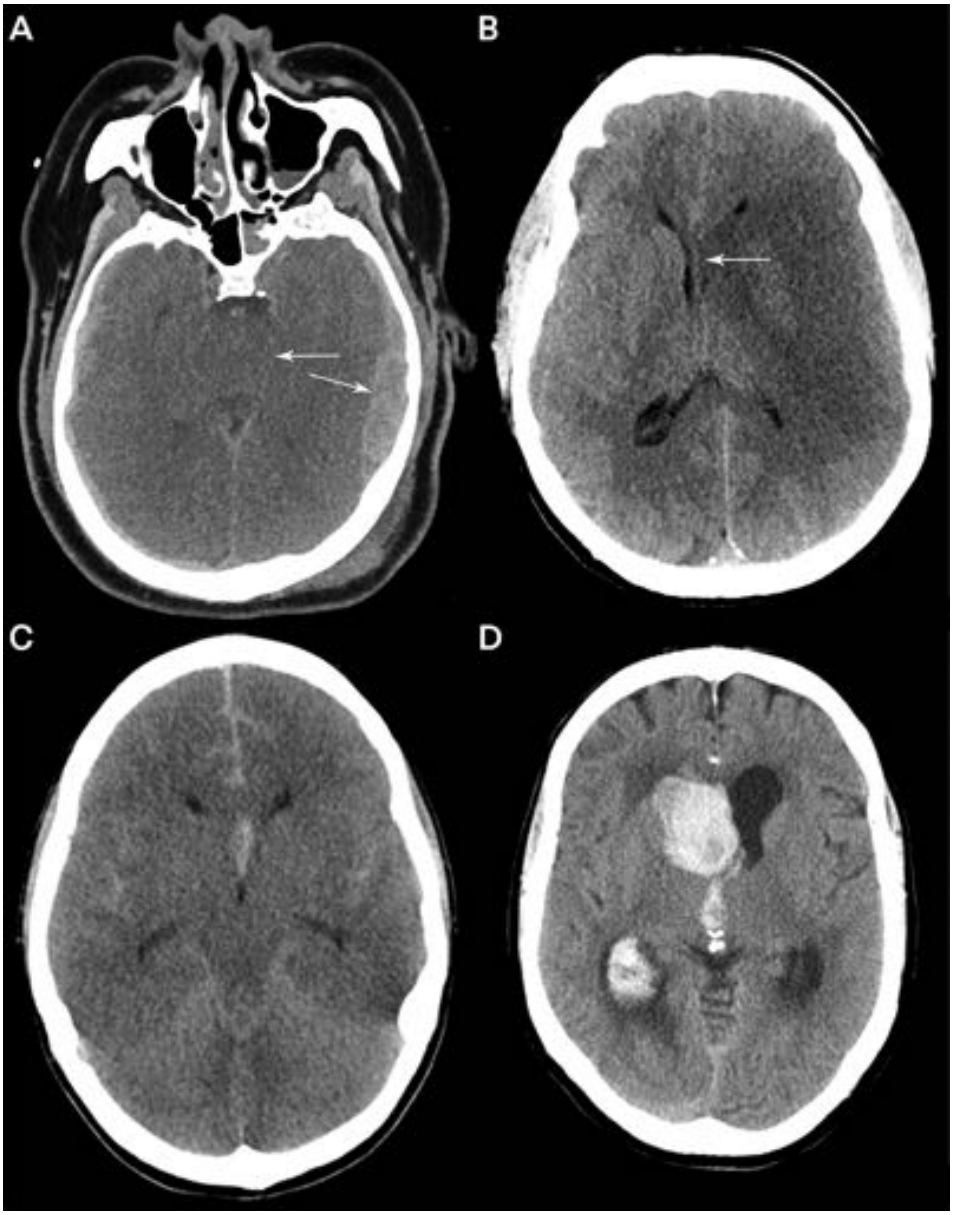

FIGURE 6-2

Select causes of coma demonstrated by CT scan. Axial noncontrast images show epidural hematoma (*A, lower arrow*) causing lateral brain displacement with upper brainstem compression (*A, upper arrow*), malignant middle cerebral artery territory infarction with subfalcine herniation (*B, arrow*), subarachnoid hemorrhage with global brain edema (*C*), and right caudate hemorrhage with extensive intraventricular extension and hydrocephalus (*D*).

disorder that is causing the comatose state, in which case initiating treatment to correct them would be futile, if not detrimental. Until more definitive information is acquired, it is advisable to be conservative with the interpretation of EEG abnormalities in patients who are comatose.

Differential Diagnosis

My mantra when evaluating coma of unclear etiology is "Think of treatable causes first!" Many treatable causes of coma require emergency treatment to avoid poor outcomes; therefore, failure to identify these causes in a timely manner can have

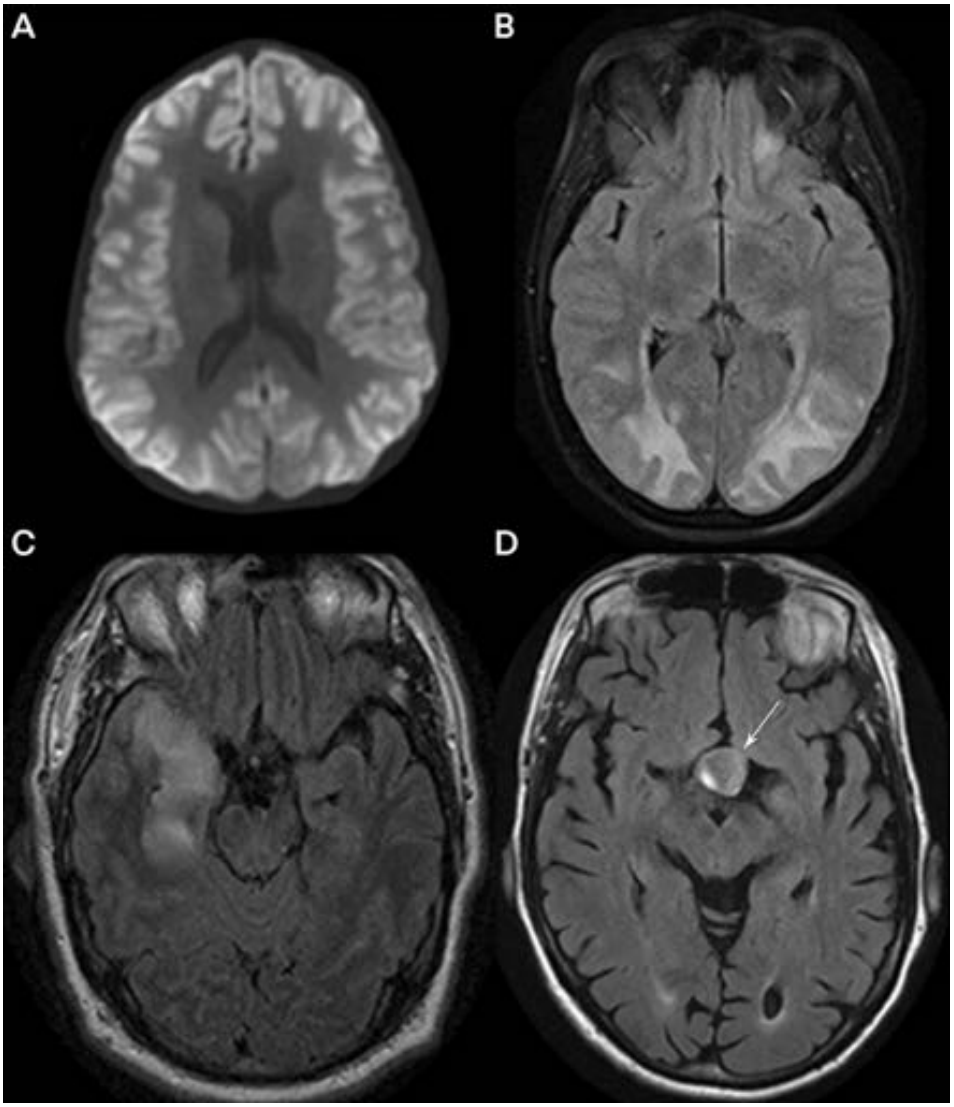

FIGURE 6-3

Select causes of coma demonstrated by axial MRI. *A*, Diffusion-weighted image (DWI) shows diffuse cortical injury after prolonged cardiac arrest. *B*, Fluid-attenuated inversion recovery (FLAIR) image shows vasogenic edema in the posterior head regions in a patient with posterior reversible encephalopathy syndrome (PRES). *C*, FLAIR image shows right temporal swelling in a patient with herpes simplex virus type 1 encephalitis. *D*, FLAIR image shows pituitary apoplexy (*arrow*).

KEY POINTS

- **When evaluating coma of unclear etiology, always think of treatable causes first.**
- **Do not assume coma is irreversible when the cause remains indeterminate.**

devastating consequences (CASE 6-1).[4,14] Some of the most notable examples are basilar artery occlusion, status epilepticus, fulminant bacterial meningitis, severe herpes simplex virus encephalitis, hydrocephalus, venous sinus thrombosis, some intoxications, and brain herniation from an excisable mass or extraaxial fluid collection.

Recognizing severe irreversible damage and spontaneously reversible causes has prognostic implications and may avoid unnecessary additional testing and empirical treatment attempts. Because outcomes generally should not be affected by a delayed etiologic diagnosis, or the evolution of the case, or the emergence of new information, testing can be more conservative in these instances. In fact, time itself may clarify the etiology. Coma should never be assumed to be irreversible as long as the cause remains indeterminate. Failure to recognize

CASE 6-1

A 58-year-old man with multiple poorly controlled vascular risk factors was brought to the emergency department with acute diplopia, dysarthria, and right hemiparesis. He arrived 45 minutes after symptom onset, and, shortly after arrival, he developed left hemiparesis, then became comatose and was emergently intubated.

Examination showed slight anisocoria with preserved reactivity, absent corneal and oculocephalic reflexes, and bilateral extensor responses to pain (Full Outline of UnResponsiveness [FOUR] score E0, M1, B2, R1). Head CT showed no acute parenchymal changes, but CT angiography confirmed the clinical suspicion of basilar artery occlusion.

He was immediately taken to the angiographic suite, where recanalization was rapidly achieved (FIGURE 6-4). By the following day, he was fully awake and had a moderate right hemiparesis and a left sixth nerve palsy. Subsequently, he was successfully extubated but required a percutaneous gastrostomy. Three months later, he was swallowing well, his diplopia was nearly resolved, and his hemiparesis had improved.

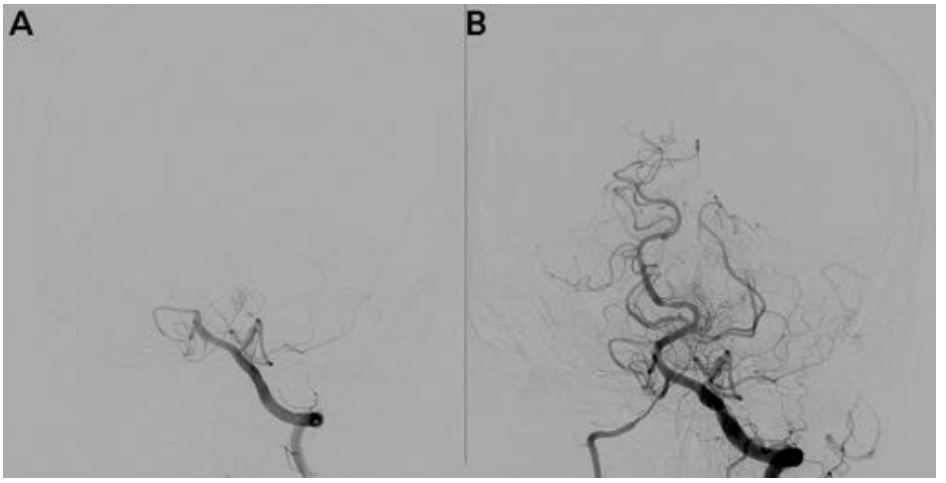

FIGURE 6-4
Angiogram of the patient in CASE 6-1. Before (*A*) and after (*B*) recanalization of the basilar artery occlusion.

COMMENT

Basilar artery occlusion is a paradigmatic example of a treatable cause of coma compatible with a favorable prognosis but only if treated without any delay. The progression of the deficits and the physical findings in this case were sufficient to have a very strong suspicion of the correct diagnosis. Focused testing and an immediate therapeutic decision resulted in a good recovery; however, if not recognized and diagnosed early, major damage to the patient inevitably occurs.

spontaneously reversible causes, such as residual effects of sedative drugs in patients who are critically ill with impaired clearance, may result in misguided prognosis and premature withdrawal of life-sustaining measures.

The differential diagnosis of coma differs considerably depending on where the patient is when coma is first noticed. In patients who are found comatose, a cerebrovascular event, unwitnessed trauma, seizure, cardiopulmonary arrest, fulminant CNS infection, sepsis, and intoxications should be primarily suspected. In patients who become comatose in the hospital, the most common causes are toxic (eg, sedatives, opiates) and metabolic derangements, which may be compounded by sepsis and hypoperfusion from shock. Postoperative coma is also often due to residual effects of medications, but anoxic-ischemic damage, stroke, and nonconvulsive seizures also deserve careful consideration. After neurosurgery, tension pneumocephalus should be added to the differential. Cerebral fat embolism can occur with orthopedic surgeries involving long bones, while air embolism can be a complication of complex cardiovascular operations.

KEY POINTS

- Treatable causes of coma most often represent a medical emergency.
- The value of pharmacologic or nonpharmacologic neurostimulation for coma recovery is unproven.
- The prognosis of coma depends mostly on its cause and duration.

Therapeutic Management

After ensuring that the patient's ventilation and oxygenation are adequate and the blood pressure is sufficient for organ perfusion, acute management depends on the known or suspected cause of the coma. Treatable causes demand emergent therapeutic interventions (TABLE 6-7).[4,14] Other general principles to follow include giving thiamine before administering dextrose, remembering that administration of flumazenil (to reverse benzodiazepine effect) may be complicated with seizures, and being aware that the effects of naloxone (to reverse opiate effect) and flumazenil are transient.

Patients who remain comatose but have conditions that may improve over time need intensive care to prevent additional brain injury and systemic complications. Secondary brain injury can result from anoxia, ischemia, herniation, intracranial hypertension, prolonged seizures, hypoglycemia, prolonged high fever, and any other derangements that may induce cerebral energy failure (ie, energy demand that is greater than the energy supply). Targeted temperature management to 33°C (91.4°F) or 36°C (96.8°F) (both temperature targets having been found equivalent in a solid randomized controlled trial)[15] followed by strict avoidance of fever should be part of the standard care of patients who remain comatose after cardiopulmonary resuscitation.[16] Patients who are comatose are at increased risk of multiple systemic complications, including infections (most commonly aspiration and ventilator-associated pneumonia, urinary tract infections related to indwelling catheters, and bacteremia related to central venous catheters), venous thromboembolism from immobility, skin breakdown, eye injury from exposure, and malnutrition, among others.

The alternative of trying some form of neurostimulation to improve alertness is a subject of debate. In a randomized controlled trial, amantadine was shown to accelerate recovery of consciousness after traumatic brain injury but without improving overall outcomes upon further follow-up.[17] Other medications, such as zolpidem, fluoxetine, methylphenidate, and other dopaminergic agents, are only supported by anecdotal reports. The value of deep brain stimulation remains unproven.

Prognosis

The prognosis of coma depends on its cause and duration. Prognosis after anoxic brain injury is generally poorer than for other causes of coma,

particularly trauma. Yet, prognosis after cardiac arrest is improving. For more information on management of coma after cardiac arrest, refer to the article "Management of Comatose Survivors of Cardiac Arrest" by David B. Seder, MD, FCCP, FCCM, FNCS,[18] in this issue of *Continuum*. Rapidly reversible causes, even if initially severe, can have an excellent prognosis if patients have no substantial residual brain injury (CASE 6-2). In general terms, it is true that the longer the duration of coma, the lower the chances of regaining consciousness. Yet, some patients may have a good outcome after a delayed

TABLE 6-7 **Main Treatable Causes of Acute Coma and Their Treatments**

Cause	Treatment
Basilar artery occlusion	IV thrombolysis, mechanical thrombectomy
Massive hemispheric infarction	Hemicraniectomy (if indicated)
Status epilepticus	Antiseizure medications
Intraparenchymal mass lesions	Surgery, osmotherapy, corticosteroids (only if edema is vasogenic)
Extraaxial collections	Surgery
Acute hydrocephalus	Ventricular drainage
Bacterial meningitis	Antibiotics and corticosteroids
Herpes simplex virus encephalitis	Acyclovir; consider antiseizure medications
Autoimmune encephalitis	Methylprednisolone, plasma exchange, or IV immunoglobulin (IVIg)
Venous sinus thrombosis	Anticoagulation, consider local infusion of thrombolytic agent
Posterior reversible encephalopathy syndrome (PRES)	Blood pressure control, discontinuation of possible culprit drugs, antiseizure medications (if seizures)
Air embolism	Consider hyperbaric oxygen (benefit possible but unproven)
Drug intoxications	Stop offending drugs and administer antidotes when available
Hypercapnia	Mechanical ventilation
Carbon monoxide poisoning	Normobaric or hyperbaric oxygen
Hypoglycemia	Dextrose preceded by thiamine
Diabetic coma	Insulin, fluids
Uremia	Dialysis
Hyperammonemia	Lactulose, rifaximin
Pituitary apoplexy	Corticosteroids, possible surgery
Myxedema	Thyroid hormone
Wernicke encephalopathy	Thiamine
Extreme hypothermia	Slow rewarming

IV = intravenous.

recovery of consciousness, most notably young patients with drug intoxications.[19] Favorable functional outcome is possible even after very prolonged refractory status epilepticus.[20] Some patients with autoimmune encephalitis may be comatose for many days and then experience a dramatic recovery with aggressive immune treatment.[21] Clinicians should be particularly cautious when estimating prognosis after severe traumatic brain injury in young patients; in these situations, progressive recovery of consciousness remains possible months after the injury.[22]

Prognostication in coma should be done cautiously and with distinct attention to the inciting cause, secondary complications (especially anoxia-ischemia), proven structural damage, and the patient's age and previous condition. Discussions with families regarding the optimal level of care for each patient should always incorporate any previously expressed patient wishes or, alternatively, the most likely patient preference in such a situation as understood by the family.

CASE 6-2

A 35-year-old woman presented to the emergency department with headache and nausea. She was treated with analgesic and antiemetic medications and was discharged home. Over the next 24 hours, she developed worsening headache and neck pain, vomiting, and rapid decline in her level of consciousness. She was taken back to the same emergency department. A head CT scan was unremarkable, and she was transferred to a tertiary care center. Before transportation, she needed to be intubated for airway protection.

On arrival at the tertiary care center, she was febrile, tachycardic, and hypotensive. Neurologic examination showed coma with preserved brainstem reflexes and bilateral withdrawal responses to pain in her arms with diffusely increased muscle tone (Full Outline of UnResponsiveness [FOUR] score E0, M2, B4, R1), and she had marked neck stiffness. She was immediately started on ceftriaxone, vancomycin, acyclovir, and dexamethasone. After review of the initial head CT scan, she had a lumbar puncture, and the CSF demonstrated pleocytosis with high protein and mildly low glucose. Gram stain demonstrated gram-positive cocci, and cultures rapidly grew *Streptococcus pneumoniae*. Within 24 hours of starting antibiotics, the patient began to improve, and she eventually made a full recovery.

COMMENT

Coma from central nervous system infection is a medical emergency. In this case, prompt treatment of the acute bacterial meningitis allowed a complete recovery, but any delay in diagnosis or empiric treatment could have been catastrophic. While signs of sepsis and neck stiffness were clear indicators of the correct diagnosis in this case, I have seen cases of severe acute meningitis in which sepsis was attributed to the wrong source and the stiffness was incorrectly blamed on another cause, such as a presumed drug intoxication. This case also illustrates that a focused history and examination can confidently guide additional testing.

KEY POINTS

- Prolonged disorders of consciousness (longer than 28 days) are typically the result of widespread brain damage.
- Prolonged disorders of consciousness constitute a spectrum that includes vegetative state (also referred to as unresponsive wakefulness syndrome) and minimally conscious state.
- Although the problem is improving, practice variations in the determination of brain death continue to occur across different states and countries.
- The diagnosis of brain death demands an established cause of irreversible coma, the absence of confounding factors, the complete absence of motor response and brainstem reflexes, and no breathing efforts on a formal apnea test.

Prolonged and Chronic Disorders of Consciousness

Patients with impaired consciousness lasting more than 28 days are operationally categorized as having a prolonged disorder of consciousness. These patients typically have widespread cerebral damage and develop substantial brain atrophy over time.[23] Depending on severity, the disorder can be classified as *vegetative state* or *minimally conscious state*. Recently, the term *unresponsive wakefulness syndrome* has been proposed to replace the designation of vegetative state.[24] Vegetative state, or unresponsive wakefulness syndrome, is characterized by spontaneous eye opening and sleep-wake cycles without any purposeful behavior suggestive of awareness of self or the environment. When such purposeful behavior becomes apparent, the patient has recovered consciousness. If the patient continues to have severe alteration of consciousness but exhibits purposeful behaviors, even if briefly, subtly, or inconsistently, the patient is said to be in a minimally conscious state. Subcategories of the minimally conscious state have been recently introduced: minimally conscious state plus, when the patient regains language function (receptive, expressive, or both), and minimally conscious state minus, when the signs of conscious awareness do not include language (but can include, for example, visual tracking, object manipulation, or affective reactions to external stimuli). Emergence from a minimally conscious state is characterized by recovery of functional communication (verbal or gestural) or functional use of objects.

The distinction between vegetative state/unresponsive wakefulness syndrome and minimally conscious state can be challenging at the bedside. There are several standardized neurobehavioral assessment tools (such as the Coma Recovery Scale-Revised)[25] that have been validated for prolonged disorders of consciousness, and they should be preferentially used and serially repeated for the evaluation of these patients (**SDC APPENDIX A**, *links.lww.com/CONT/A256*).[26] Furthermore, recent research using functional MRI (fMRI) and fludeoxyglucose positron emission tomography (FDG-PET) imaging indicates that a small minority of patients classified as vegetative state/unresponsive wakefulness syndrome actually show changes in brain metabolism during mental activation tasks compatible with a minimally conscious state.[1,27] These findings might predict that a patient may later have behaviorally evident recovery of consciousness.[26] Yet, it is important to clarify that the potential value of these investigations has only been shown in subjects with prolonged disorders of consciousness and not in patients with acute coma.

When medically stable, patients with prolonged disorders of consciousness should be referred to centers with multidisciplinary teams specialized in the monitoring of delayed complications and the rehabilitative care of these types of cases.[26]

BRAIN DEATH

Brain death is the term often used for death determined by neurologic criteria. It refers to a condition in which systemic circulation is preserved but no evidence of any brain or brainstem function is present. The diagnosis does not permit ambiguity. The implications are final, and, therefore, the diagnosis must be definite and unquestionable.

Unfortunately, while the concept of brain death is broadly accepted across the world, the conditions required for its determination vary in different countries and even, to a lesser degree, across US states.[28,29] Uniformity in hospital policies

is growing across large institutions in the United States, but some variability persists.[30] Thus, physicians should be cognizant of the local policies and specific legal requirements where they practice. Various national and international health organizations, including the AAN, are actively working to achieve a consensus on how to determine brain death regardless of where the patient is physically located. Also, while one examination is sufficient to declare brain death in adults in most US states, a second examination by a different physician is required in pediatric cases, with the two examinations separated by 24 hours when the patient's age is between 37 weeks gestation and 1 month and separated by 12 hours when the patient's age is between 1 month and 18 years.[31]

Clinical Criteria

In most instances, the diagnosis of brain death can and should be established by the findings of the bedside neurologic examination. The AAN guidelines provide a clear description of the steps that are necessary to determine brain death with full reliability (FIGURE 6-5) (SDC APPENDIX B, *links.lww.com/CONT/A257*).[2]

Before proceeding with the clinical examination, two prerequisites must always be met: (1) establish an irreversible cause of coma and (2) confirm the absence of confounding factors, such as prescription and recreational drugs that can depress brain function, pharmacologic neuromuscular blocking effect,

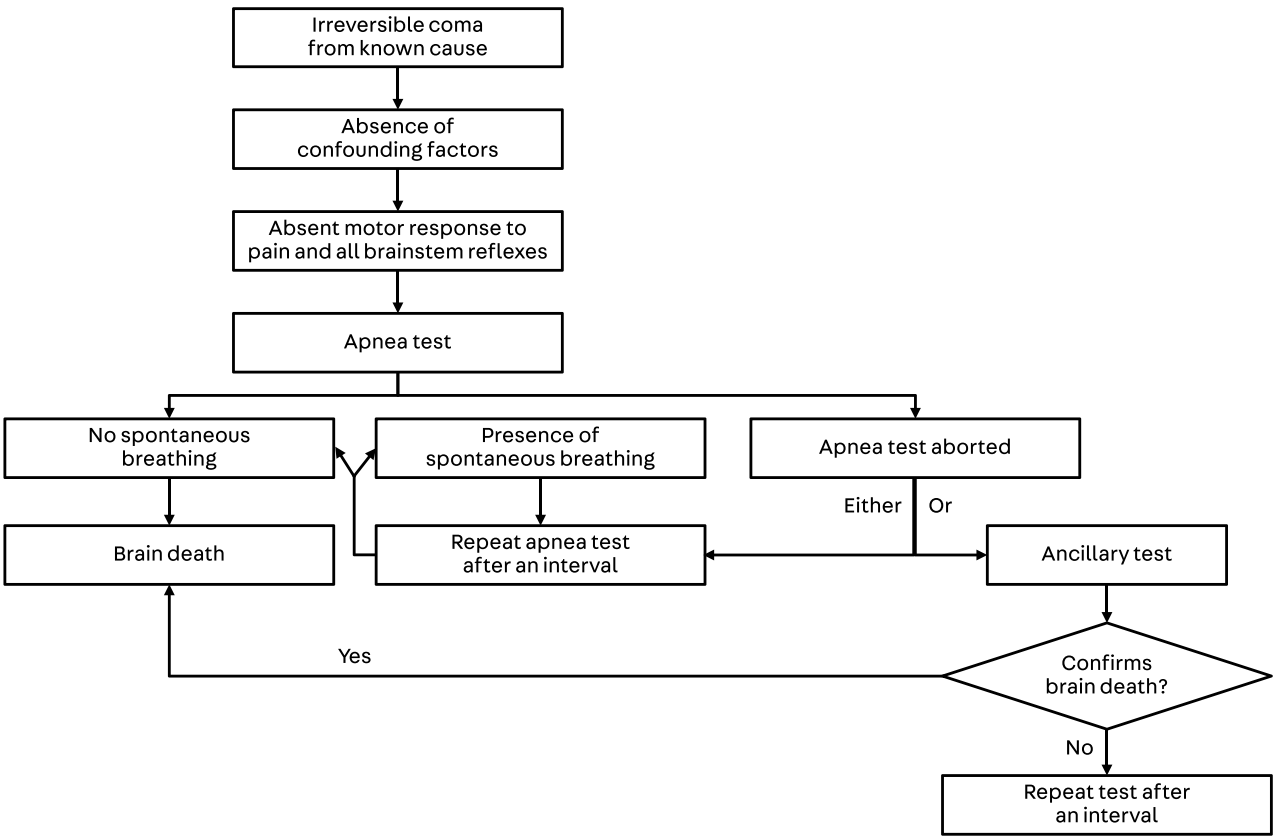

FIGURE 6-5
Schematic representation of the steps required for the determination of brain death.

hypothermia, hypotension, and major metabolic derangements (electrolytes, acid base, or endocrine) (CASE 6-3).

The neurologic examination to assess for brain death should be performed in a rigorous stepwise manner, with strict attention to detail.[32]

CONFIRM COMA. The patient should show no evidence of responsiveness to any stimulation, whether eye opening, eye movements, or any other motor response that cannot be explained by spinal reflexes.

CONFIRM ABSENCE OF BRAINSTEM REFLEXES. The patient's pupils should be midsized and nonreactive to bright light. Corneal stimulation should not elicit blinking or any other response. On oculocephalic (only if cervical spine integrity allows it) and oculovestibular (ie, cold caloric) reflex testing, the eyes should not move. Facial muscles should not contract upon pressure applied to the temporomandibular joints, gag reflex should not be activated by stimulation of the posterior pharyngeal wall, and cough reflex should be not be elicited despite stimulation of the carina with a suctioning catheter.

CONFIRM APNEA. Complete absence of a breathing drive despite high $PaCO_2$ should be established by a formal apnea test. The apnea test itself has a set of prerequisites and rigorous steps that must be respected, as detailed in TABLE 6-8.

CASE 6-3

A 72-year-old man was brought to the emergency department after a witnessed cardiac arrest from ventricular fibrillation. After multiple electric shocks and prolonged advanced cardiopulmonary resuscitation efforts, he regained spontaneous circulation but remained comatose. He was treated with a targeted temperature management protocol during the first 24 hours using a target temperature of 33°C (91.4°F). Because of shivering, he was given neuromuscular blocking agents and propofol. EEG performed through rewarming showed a burst-suppression pattern. He had a history of diabetic nephropathy and developed superimposed acute kidney injury. Elevated liver transaminases were also noticed. Early on day 3 after the arrest, the cardiology team questioned whether the patient might be brain dead.

COMMENT

This case illustrates the common scenario of a patient who is comatose with very poor prognosis for whom a team of non-neurologists brings up the possibility of brain death without considering the presence of confounding factors. After therapeutic hypothermia, the neurologic examination is often contaminated by the lingering effects of sedative drugs, which may be prolonged because of delayed clearance from kidney and liver dysfunction and hypothermia itself. In the case presented, brain death could not be determined even if the examination had shown the absence of brainstem reflexes and motor responses to pain. Thus, in this situation, it would be incorrect to proceed with a formal evaluation for brain death.

Apnea tests are feasible in the majority of patients with irreversible coma, even among most patients with severe cardiopulmonary disease, when these steps are carefully followed.[33] Ensuring steady delivery of oxygen and having immediate access to vasopressors (most of these patients are already on vasopressors by the time of the apnea test) are essential conditions for successful completion of the test. In the rare instances that the test must be aborted because of hypotension or hypoxemia, it is reasonable to consider a new attempt after adequate preparation. The time of conclusion of the apnea test, which is when the $PaCO_2$ is shown to be sufficiently high, represents the legal time of expiration. After that, state laws require the physician to inform the local organ procurement organization.

Ancillary Tests

Several ancillary tests can be used to confirm brain death, but all have limitations.[34] They can complement the neurologic examination but should never replace it. Their most appropriate role is when certain aspects of the neurologic examination cannot be performed (eg, when an apnea test cannot be safely completed in a patient with severe pulmonary contusions and acute respiratory distress syndrome). However, some countries and a few US states require one of these tests for confirmatory purposes in all cases of brain death determination.

EEG, cerebral scintigraphy with nuclear scan, and catheter cerebral angiography are the traditional ancillary tests, but transcranial Doppler and, more recently, CTA have been added to the list.[35] Specific considerations apply to the performance of all these tests for the indication of possible brain death

The Apnea Test TABLE 6-8

Prerequisites

- $PaCO_2$ between 35 mm Hg and 45 mm Hg
- Systolic blood pressure ≥100 mm Hg with or without vasopressors
- Administer 100% oxygen for at least 10 minutes (ideal PaO_2 >200 mm Hg with positive end-expiratory pressure ≤5 cm H_2O)
- Absence of clinical signs of intravascular volume contraction

Steps

- Disconnect the patient from the ventilator
- Deliver oxygen at 6 L/min through a catheter advanced through the tracheal tube until close to the carina
- Look carefully for any respiratory movements while monitoring pulse oximetry and blood pressure
- Abort and reconnect to the ventilator if evidence of respiratory movements, refractory hypotension (systolic blood pressure <90 mm Hg) or worsening hypoxemia (pulse oximetry <85%)
- If no respiratory movements after approximately 8 minutes, obtain arterial blood gases
- Apnea is established if $PaCO_2$ ≥60 mm Hg (or 20 mm Hg greater than baseline)

$PaCO_2$ = partial pressure of carbon dioxide, arterial; PaO_2 = partial pressure of oxygen, arterial.

(TABLE 6-9). False negatives and, most concerningly, false positives (ie, results that would falsely support the diagnosis of brain death) have been reported with these tests when compared to the gold standard of physical examination. Therefore, it is essential that their pitfalls be carefully considered.[34]

Common Pitfalls and Persistent Controversies

In addition to the limitations and potentially false results of ancillary tests, several other pitfalls must be kept in mind. Inadequate consideration of confounding

TABLE 6-9 Ancillary Tests for the Determination of Brain Death

Test	Testing Conditions	Diagnostic Finding Compatible With Brain Death	Possible Pitfalls
EEG	Minimum of eight electrodes: Interelectrode distance ≤10 cm Interelectrode impedance between 100 and 10,000 Ω Sensitivity ≥2 μV High-frequency filter <30 Hz and low-frequency filter >1 Hz Duration ≥30 minutes	Complete absence of cerebral electric activity, including lack of reactivity to intense, painful, visual, and auditory stimulation	Electric artifacts (common in the intensive care unit); mostly evaluates the cortex
Nuclear medicine scan[a]	Isotope injection within 30 minutes of reconstitution; anterior and bilateral planar image counts upon injection and after 30 minutes, 1 hour, and 2 hours	No brain perfusion (hollow skull)	Incorrect injection (can be avoided by confirming uptake in the liver)
Transcranial Doppler	Bilateral transtemporal and transforaminal insonation; transorbital window insonation can be considered	Reverberating arterial flow or small peaks in early systole	Lack of reliable signal because of poor temporal bone window; highly dependent on skill of operator; absence of flow is not reliable because it may be due to poor windows or poor technique
Catheter angiography	Contrast injection in the arch and under high pressure	Absence of flow in intracranial arteries	Inadequate pressure upon injection; partial filling of intracranial arteries without reaching perfusing branches
CT angiography	Contrast injection from a peripheral vein with a pressure injector; arterial and venous phases should be imaged	Absence of flow in distal middle cerebral arteries	May be unreliable in low-flow states (delayed perfusion may be missed by usual timing of image acquisition); sensitivity is limited when only using arterial filling as diagnostic criterion; absent flow in internal cerebral veins may increase sensitivity

CT = computed tomography; EEG = electroencephalogram.
[a] Cerebral scintigraphy with technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO).

factors, especially residual effects of drugs (CNS depressants and neuromuscular blocking agents), is probably the most common. When in doubt, measurement of serum levels of administered drugs is always advisable. Misidentification of spinal reflexes as motor responses is another common problem. Movements generated by spinal reflexes are provoked by neck flexion or stimulation below the neck but not by stimulation above the neck. They can have various appearances (most frequent are leg triple flexion, finger flexion or extension, or slight head turning),[36] but in the same patient, they are always stereotypical. Therefore, repeated testing may aid in their differentiation from motor responses generated higher in the neuraxis; however, stereotypy itself is not pathognomonic of spinal reflexes because it can also be observed with extensor or flexor posturing. Experience is necessary for reliable distinction. So-called "brain death mimics" exist (eg, Guillain-Barré syndrome, organophosphate poisoning, lidocaine toxicity, baclofen overdose), but attentive clinicians should be able to recognize them. Another common problem is inadequate preparation of the patient before starting the apnea test. Insufficient preoxygenation, lack of access to titratable vasopressors, and failure to correct volume depletion can result in failure to complete the apnea test while exposing organs to potential injury from hypoperfusion and hypoxemia.

Lingering controversies persist. Some consider that ancillary tests are indicated to evaluate supratentorial function in patients with devastating brainstem damage. The ancillary test would be necessary to confirm that these patients are not in a complete locked-in state. In these cases, supratentorial blood flow may be present initially but becomes absent within a few days at the latest.[37] Exceptional cases of erroneous clinical diagnosis of brain death have been reported, but in all instances, confounding factors that failed to be recognized could explain the diagnostic error.[38] While all major religions across the world endorse the concept of brain death, small cultural and religious groups continue to challenge the validity of the concept.[39] Clearer and more consistent laws are the only way these rare and very problematic disputes may be avoided in the future.

KEY POINTS

- **Angiography, nuclear scans, EEG, and transcranial Doppler are ancillary tests that can be used to confirm brain death, but they all have limitations.**
- **The most appropriate use of ancillary tests to confirm brain death is to complement the neurologic examination when certain aspects of the examination (such as the apnea test) cannot be performed.**
- **Not recognizing confounding factors (especially the residual effects of central nervous system depressants) is a common pitfall in brain death evaluations.**
- **The concept of brain death is accepted by all major religions, but small cultural and religious groups continue to challenge the validity of the concept.**

CONCLUSION

The evaluation of the patient who is comatose requires attention to detail and a methodical approach to avoid missing treatable causes and secondary injurious complications. History and examination should guide additional testing to navigate across the multiple possible causes of coma. Prognosis depends primarily on the cause of the coma and should be delivered cautiously because delayed recovery is possible in various situations.

Brain death can only be diagnosed after concluding that a patient has a known cause of irreversible coma and proving the complete absence of all signs of brain and brainstem function. Confounding factors (such as drug effects and hypothermia) must always be considered and specifically excluded. In most instances, brain death can and should be determined based on neurologic examination; use of ancillary tests is generally unnecessary.

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