

Initial Diagnosis and Management of Coma



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KEYWORDS

• Coma • Coma mimics • Pathophysiology

KEY POINTS

- Coma is a life-threatening process that requires immediate stabilization and a structured approach to diagnosis and management.
- The differential diagnosis for coma is long, but is often divided into structural vs. diffuse neuronal dysfunction; the latter is subdivided into toxic vs. metabolic.
- When available, historical information may be of great use in determining the etiology of coma; in all cases, a focused physical examination can help greatly refine the differential diagnosis.
- The definitive treatment of patients with coma is ultimately disease-specific.

INTRODUCTION

Many patients present to the emergency department with an alteration in mental status simply as a complication of many serious illnesses. A subset of these patients will present comatose, a clinical state that is a true medical emergency. Although coma is a relatively rare presenting condition in the emergency department, patients who present with coma are often in extremis and necessitate immediate evaluation and stabilization.

The approach to coma by the emergency physician is described, beginning with a discussion of pathophysiology and cause. Then, the practical clinical aspects of coma are addressed, including initial stabilization, obtaining the correct historical information, performing a thorough physical examination, ordering appropriate testing and imaging studies, and providing appropriate treatment.

PATHOPHYSIOLOGY

A neuronal network in the dorsal pons and midbrain give rise to the ascending reticular activating system (ARAS), which is responsible for arousal.¹ Neurons from these centers

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run together through the thalamus and then to the bilateral cerebral cortex; the cortex controls sensory processing and understanding, which generates awareness.^{2,3} Coma results from an impairment of this axis by a process that affects the brain's arousal center, consciousness center, the tracts that connect them, or some combination thereof. Patients are, therefore, not aware and not awake. Importantly, coma from cortical impairment can only result from a bilateral insult; unilateral cortical deficits do not cause coma. Prolonged coma may result in awakening cycles (eyes open coma) without awareness. Because the comatose state is difficult to quantify, some patients diagnosed as comatose may be minimally aware (minimally conscious state) and others may be more aware than can be assumed or tested.

Although the final common physiologic pathway of coma is neuronal dysfunction in the ARAS-thalamic-cortical pathway, it is useful to subdivide the pathophysiology into structural versus diffuse neuronal dysfunction. Structural causes of coma are defined as those that precipitate cellular dysfunction through a mechanical force, such as pressure on key area or a blockade of delivery of critical cellular substrate. Diffuse neuronal dysfunction precipitates coma by abnormalities only at the cellular level and may be further divided into two general categories: toxic and metabolic. In a toxin-induced coma, an exogenous substance is responsible for the clinical findings; in a metabolic coma, a perturbation of an endogenous process, such as temperature or sodium regulation, has gone awry.

This classification, although useful, does have limitations. A metabolic process, such as hypoglycemia or hypoxia, may initially produce coma through diffuse neuronal dysfunction; however, if the process is uncorrected and cell death occurs, the cause of coma becomes structural. Similarly, a diffuse neuronal process, such as cerebral edema, may become a structural problem if the edema occludes vessels in the posterior circulation and produces brainstem ischemia.

CAUSES

A causal overview of coma is presented in **Table 1**, categorized based on this logic, and includes coma mimics, which are several disorders that may be easily mistaken

| Coma | | | |
|------------------------------|-----------------------|-----------------------|------------------------------|
| Diffuse Neuronal Dysfunction | | | |
| Structural | Toxic | Metabolic | Coma Mimics |
| Neoplasia | Sedative-hypnotics | Respiratory | Locked-in syndrome |
| Hydrocephalus | agents | insufficiency | Neuromuscular paralysis |
| Intracranial | Opioids | Dysthermia | Akinetic mutism |
| hemorrhage | Dissociative agents | Dysglycemia | Psychogenic unresponsiveness |
| Vascular | Carbon monoxide | Electrolyte disorders | |
| occlusion | Toxic alcohols | Infection | |
| | Antidepressants | Hypothyroidism | |
| | Antiepileptics | Thiamine deficiency | |
| | Agents of | Nonconvulsive status | |
| | histotoxic hypoxia | epilepticus | |
| | Simple asphyxiants | | |
| | Serotonin syndrome | | |
| | Neuroleptic malignant | | |
| | syndrome | | |
| | Clonidine | | |

for coma but do not involve interruption of the ARAS-thalamic-cortical pathway. For the purposes of this article, the focus is on relatively common entities that may present with coma, rather than those that are uncommon or in which coma is a late finding.

STRUCTURAL CAUSES OF COMA

Tumors

Tumors may cause coma by exerting pressure on either a key area (eg, the brainstem) or by causing a diffuse increase in intracranial pressure. More commonly, however, patients with tumors have a slow progression of neurologic findings. Abrupt onset of coma in such patients often results from hemorrhage into an expanding mass. Even small tumors, however, may cause obstructive hydrocephalus or focal infarctions, each of which may in turn lead to the relatively abrupt onset of coma.

Acute Hydrocephalus

There is approximately 100 to 150 mL of cerebrospinal fluid (CSF) in the adult brain. CSF is produced predominantly in the choroid plexus, circulates through the ventricular system, and empties into the subarachnoid space where it is absorbed predominantly into the venous system through the arachnoid villi.⁴ Occlusion of this flow via tumor, clotting of intraventricular blood, or dysfunction of the arachnoid villi may lead to an increase in intraventricular CSF, with a concurrent increase in intracranial pressure and resultant coma.

Intracranial Hemorrhage

Central nervous system (CNS) hemorrhage resulting in coma may have 1 of 4 causes.

Spontaneous subarachnoid hemorrhage

Spontaneous subarachnoid hemorrhage (SAH) usually results from the rupture of an aneurysm in the Circle of Willis (often referred to as a berry aneurysm). Thunderclap headache on presentation is present in more than 95% of patients.⁵ Coma in the setting of SAH may be due to acute hydrocephalus or anoxic-ischemic injury.

Subdural hemorrhage

Subdural hemorrhage (SDH) is an accumulation of blood between the dura and the arachnoid membrane. SDH is often associated with a trauma but may also be associated with low intracranial pressure, as occurs after lumbar puncture.⁶ SDH may occur because of either shearing of bridging veins⁷ or arterial interruption.⁸ The use of both antiplatelet agents and anticoagulants increase the risk of SDH.⁹ SDH may produce a rapid shift of brain parenchyma, resulting in compression of the thalamus and pressure on the brainstem. Seizures, including nonconvulsive status epilepticus (NCSE), may mimic structural injury and are more often seen after hematoma evacuation.

Epidural hemorrhage

Epidural hemorrhage (EDH) is most often due to blunt force trauma that disrupts an epidural artery, with blood collecting in the potential space between the dura and the skull. Patients may present with initial confusion or loss of consciousness from which they recover, only to subsequently "talk and deteriorate." This lucid interval occurs in approximately half of all EDH patients.¹⁰ Coagulopathy is associated with a poorer outcome in patients with EDH.¹¹ Similar to SDH, brain parenchymal shift, brainstem pressure, and seizures may result.

Intraparenchymal hemorrhage

Intraparenchymal hemorrhage (IPH) is usually due to longstanding hypertension and associated vascular changes, although amyloid angiopathy and coagulopathy are other possible causes.¹² Coma from an IPH may be caused by the disruption of key tracts or a general increase in intracranial pressure, depending on the location of the lesion.

Vascular Occlusion

Arterial vascular occlusion may be either thrombotic or embolic; both may produce coma if critical structures are affected. Of note, arterial vascular occlusion causing coma is usually a posterior circulation event, with occlusion in the vertebrobasilar system leading to hypoperfusion of crucial structures within the ARAS. Arterial occlusion in the anterior circulation is an uncommon cause of coma because bilateral cortical disruption is required to produce the requisite depression of consciousness. This may occur, however, in patients who have suffered a stroke on one side of the brain and subsequently suffer an acute arterial vascular occlusion on the other.

DIFFUSE NEURONAL DYSFUNCTION CAUSES OF COMA: METABOLIC

Respiratory Insufficiency

Respiratory insufficiency may produce coma in two ways. First, the brain is particularly sensitive to the effects of hypoxia, with coma possible within minutes of acute oxygen deprivation. Second, hypercarbia may cause coma; the exact mechanism is unclear, but may involve an alteration in neurotransmitter levels or changes in intracranial pressure as increases in carbon dioxide levels are associated with increases in cerebral blood flow.

Dysthermia

Extremes of body temperature may accompany other primary causes of coma or be a primary cause. Although the exact temperature at which coma occurs will vary by individual, loss of consciousness in hypothermic patients generally occurs around 28°C¹³ and hyperthermia-induced coma generally does not occur below a temperature of 40°C.¹⁴

Hypertension

Rarely, severe hypertension may result in a loss of vascular epithelial integrity in small vessels of the brain, resulting in a patchwork pattern of vascular narrowing and vasodilation, resulting in cerebral edema.¹⁵ This condition, called posterior reversible encephalopathy syndrome, may present with significant alterations in consciousness.

Dysglycemia

Hypoglycemia may produce virtually any neurologic sign, symptom, or syndrome, including coma. Hypoglycemia is most common in diabetic patients who are taking hypoglycemic agents, such as insulin or sulfonylureas, and the rate of coma in such patients is about 1% to 2% per year.^{16,17} Hyperglycemia may also cause coma, most commonly in the setting of a hyperosmolar hyperglycemic state (HHS) in which glucose levels are greater than 600 mg/dL and osmolality greater than 320 mOsm/kg.¹⁸ Coma is more common in HHS than diabetic ketoacidosis (DKA). Serum osmolality is the driver of mental status changes in hyperglycemic states and HHS is associated with higher serum osmolality levels than DKA.¹⁹

Electrolyte Disorders

Disorders of sodium hemostasis, particularly when they are acute, may produce coma. Hyponatremia produces an imbalance of intracellular versus extracellular osmolality, the flow of free water into the brain parenchyma, and the development of cerebral edema.²⁰ Hypernatremia may also cause coma, and overly-rapid correction (particularly when the hypernatremia develops acutely) may lead to either demyelination or intracranial hemorrhage due to abrupt changes in intraparenchymal volume.²¹

Hypercalcemia is common in patients with advanced malignancy, occurring in 10% to 20% of such patients.²² Although the most common neurologic presentations of hypercalcemia are confusion, delirium, or lethargy, coma is reported.²³

Infection

Coma in the setting of infection may be due to one of several CNS infections. Profound coma is a rare presentation of meningitis²⁴ but is more commonly seen in fulminant cases. In one series, approximately 10% of subjects with encephalitis presented with coma (defined by the investigators as Glasgow Coma Scale [GCS] ≤ 8) and these subjects had poorer outcomes.²⁵

Systemic non-CNS infections, such as sepsis, may also produce coma. The myriad biochemical and microcirculatory changes involved in sepsis-induced coma are incompletely understood but seem to activate neuroinflammatory and ischemic pathways culminating in dysfunction of the brain parenchyma.²⁶

Thyroid Disorders

Myxedema coma is a severe form of hypothyroidism in which alterations in cerebral blood flow and glucose metabolism may lead to significant changes in mental status²⁷ and coma.²⁸ The alterations in mental status that accompany hyperthyroidism classically include nervousness and anxiety,²⁹ but decreases in mental status (which may include coma) may occur and are more common in the elderly.^{30,31}

Renal Failure

Renal failure produces neurologic findings that include uremic encephalopathy, which in severe cases may manifest as coma.³² The molecular basis of uremic encephalopathy is not fully elucidated but it is likely a multifactorial process that includes the accumulation of false neurotransmitters.

Hepatic Failure

Hepatic failure may lead to an encephalopathic state caused by either an accumulation of endogenous toxins (including ammonia) or cerebral edema.³³

Hyperammonemia

Although hyperammonemia is a common finding in hepatic failure, nonhepatic hyperammonemia may cause coma as well. Valproic acid therapy in the setting of carnitine deficiency, infection with urease-producing bacteria, recent surgery (particularly lung transplantation, bariatric surgery or ureterosigmoidostomy), hyperalimentation, and errors of metabolism are also potential causes.³⁴

Thiamine Deficiency

Thiamine deficiency is a common problem in malnourished patients. In the emergency department, thiamine deficiency is of particular concern in patients with alcohol-related presentations, not only in alcoholics but in binge drinkers as well.³⁵ Severe

thiamine deficiency, usually seen in the context of alcoholism, may lead to Wernicke encephalopathy (characterized by encephalopathy, oculomotor dysfunction, and gait ataxia) or Korsakoff psychosis (a chronic amnesic condition). Coma as a presenting symptom of thiamine deficiency, however, is very uncommon.^{36,37}

Nonconvulsive Status Epilepticus

NCSE is an epileptogenic condition in which the classic manifestations of seizure (eg, focal or general motor activity) are absent. NCSE may be mistaken for coma or unresponsiveness, and is an under-recognized cause of altered mental status in the emergency department.³⁸

DIFFUSE NEURONAL DYSFUNCTION CAUSES OF COMA: TOXINS

Sedative-Hypnotic Agents

Sedative-hypnotic agents are a broad class of drugs that include ethanol, benzodiazepines, barbiturates, baclofen, gamma-hydroxybutyrate, and others. Most sedative-hypnotic agents act by facilitating the effect of the neurotransmitter gamma-aminobutyric acid (GABA), hyperpolarizing neurons either through an increase in chloride conductance (GABA_A)³⁹ or through an increase in potassium conductance (GABA_B).⁴⁰ Ethanol, in addition to interacting with the GABA system,⁴¹ also produces some effects via interference with the excitatory neurotransmitter N-methyl-D-aspartate (NMDA).⁴²

Opioids

Opioids (ie, heroin, morphine, oxycodone, hydrocodone, and others) may produce profound decreases in mental status, including coma, in addition to other clinical findings such as respiratory depression. Opioid receptors are coupled to G proteins, which may exert their effects via adenylate cyclase, calcium channels, or potassium channels.⁴³ Opioids have multiple receptor subtypes, with the mu receptor responsible for coma.

Dissociative Agents

Phencyclidine and ketamine depress (and therefore interrupt) thalamic-cortical tracts,⁴⁴ producing a temporary state in which cardiorespiratory functions are preserved but in which the patient is dissociated from his or her higher functions. Dissociative agents likely exert most of their effects via NMDA antagonism but also have effects on opiate receptors and sympathetic neurotransmission.⁴⁵

Carbon Monoxide

Carbon monoxide (CO) poisoning is alarmingly prevalent, accounting for approximately 50,000 visits per year to US emergency departments⁴⁶ and, in severe cases, presenting with coma.⁴⁷ CO is a complex toxin that affects oxyhemoglobin dissociation, increases oxidative stress, interrupts cellular respiration, and leads to the generation of reactive oxygen species. All of these may contribute to the development of neurologic impairment.⁴⁸

Serotonin Syndrome and Neuroleptic Malignant Syndrome

Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are distinct entities with overlapping presentations that, when severe, include profound alterations in mental status, muscular rigidity, and hyperthermia. SS results from an excess of central and peripheral serotonin activity, often when two or more serotonergic agents are

used together⁴⁹ NMS (although less well understood) likely results from central dopaminergic blockade.⁵⁰

Miscellaneous Toxins

Several other toxins may produce coma. Toxic alcohols, such as methanol and ethylene glycol, are CNS depressants that produce coma in a manner similar to ethanol. Psychiatric medications, such as tricyclic antidepressants and serotonin selective reuptake inhibitors, may produce coma as an exaggeration of their normal pharmacologic effects. Simple asphyxiants, such as nitrogen, act by displacing oxygen and producing hypoxia. Agents of histotoxic hypoxia, such as cyanide, interfere with aerobic metabolism and the generation of adenosine triphosphate. Clonidine alters central sympathomimetic neurotransmission.

Coma Mimics

Four conditions deserve mention as coma mimics. The locked-in syndrome describes paralysis of all voluntary muscles of the body save the eyes, usually as a result of ischemia or infarction to key CNS tracts often involving the pons, with preservation of consciousness and higher cortical functions.⁵¹ Neuromuscular paralysis may be iatrogenic, after the administration of succinylcholine or curare-like drugs, or may arise from varied environmental sources, such as the toxin of *Clostridium botulinum*, the venom of elapid snakes,⁵² or tetrodotoxin-producing organisms such as the blue-ringed octopus.⁵³ Akinetic mutism usually results from injury to the frontal or prefrontal motor cortex, in which patients cannot initiate voluntary motor movements.⁵⁴ In all 3 of these diseases, consciousness is preserved. The fourth coma mimic is psychogenic unresponsiveness, a complex disorder in which there is no neurologic insult; the condition resolves spontaneously.⁵⁵

INITIAL STABILIZATION

The initial stabilization of comatose patients is the same as that for that of all emergency department patients and consists of securing the patients airway (with attention to the cervical spine), breathing, and circulation.

Decisions regarding airway management are often very difficult, driven by gestalt rather than algorithmic decision making, and are based on several factors. Mechanism of coma is important; although a GCS of 8 or less in a trauma patient is often viewed as an indication for intubation,^{56,57} poisoned patients with such GCS levels can be managed without intubation and with low levels of complications.^{58,59} Monitoring concerns may also enter into the decision-making process. Patients who require significant time out of the department for diagnostic imaging, as may occur during a computerized tomography (CT) scan, may require intubation; whereas patients who remain in an acute care area might be managed expectantly, even at the same level of consciousness. Expected clinical course, particularly in poisoned patients, is also a factor. The patient with an isolated alprazolam ingestion will likely do well without intubation, whereas a patient with carbamazepine ingestion is more likely to have a complicated course and require airway intervention.

Concurrently with airway management, the cervical spine must be stabilized whenever there is a possibility that the patient's alteration in mental status has a traumatic cause. Cervical spine injuries are commonly associated with alterations mental status of traumatic cause, occurring in 5% or more of such patients.^{60,61}

HISTORY

Comatose patients by definition cannot give details of their illness, so it is crucial that the provider actively seek alternative sources of information. Emergency medical service responders often provide the most valuable information. They can relay information obtained from family members or bystanders, describe the patient's initial level of consciousness and how that has changed en route, provide a description of how the patient was found, and contribute important situational information such as the presence or absence of prescription bottles or drug paraphernalia. Ideally, the belongings of comatose patients should also be examined for clues, such as pill bottles in coat pockets or a purse, a pharmacy phone number, or a medication list in a wallet. Finally, medical alert bracelets or information from the institution's medical record may shed light on an otherwise confusing presentation.

To the extent possible, the clinician should establish the rate of progression of symptoms. Coma because of subarachnoid hemorrhage, cerebellar infarction, and IPH is usually of abrupt onset, whereas coma from infection may evolve over hours to days. Coma from poisoning may occur over minutes if caused by a large dose of drug (eg, an opioid) or a rapidly acting toxin (eg, volatilized cyanide after malicious mixing with a soft drink). Alternatively, it may occur over the course of hours if the patient over-titrates a self-administered substance (eg, ethanol) or ingests a substance that may have delayed toxicity (eg, baclofen).

Importantly, when obtaining historical information, providers must avoid the errors of premature closure and diagnostic anchoring.⁶² For example, alcohol is ubiquitous in many western countries and its presence may be coincident with, rather than causative of, coma. SDH and hypoglycemia are life-threatening causes of coma that may coexist with ethanol intoxication.^{63,64} As with any condition, physicians evaluating patients with coma must be willing to reconsider initial impressions when additional data, such as a fever or classic physical examination findings, are inconsistent with the initial working diagnosis.

PHYSICAL EXAMINATION

A complete physical examination will provide clues to the diagnosis of coma and help streamline the patient's diagnostic evaluation. Crucial physical examination findings, and the important causes of coma associated with them, are listed below.

VITAL SIGNS

Pulse

Bradycardia may occur in the context of sympatholytic drugs, such as clonidine; in the setting of sedative hypnotic toxicity, particularly with barbiturates and gamma-hydroxybutyrate; and with increases in intracranial pressure, characteristically accompanied by systemic hypertension. Tachycardia is common with psychotropic drug poisoning, ketamine intoxication, adrenergic hyperactivity from intracranial hemorrhage, and 3,4-methylenedioxymethamphetamine (MDMA) intoxication, which produces coma via symptomatic hyponatremia.⁶⁵

Blood Pressure

Hypotension may occur in sepsis and many poisonings, particularly tricyclic antidepressants, sedative-hypnotic agents, and clonidine. Hypertension is a prerequisite for the diagnosis of hypertensive encephalopathy and is common in ketamine or

phencyclidine intoxication, MDMA intoxication, and in the setting of increased intracranial pressure. In the cases of elevated intracranial pressure, the hypertension is usually accompanied by bradycardia, a combination known as Cushing response.

Respiratory Rate

Tachypnea is common with metabolic acidosis of any cause. Bradypnea may be seen in both opioid and sedative-hypnotic toxicity but is much more pronounced in the former. Bradypnea in the setting of structural CNS disease suggests medullary involvement and is often a preterminal event.

Temperature

Hyperthermia may be due to environmental exposure, infection, NMS, SS, salicylate poisoning, and several primary CNS disorders, including subarachnoid hemorrhage and hypothalamic injury. Hypothermia is commonly due to environmental exposure but may also be seen with hypoglycemia of any cause, sedative-hypnotic toxicity, hypothyroidism, and overwhelming infection.

Physical Examination

Head, eyes, ears, nose, and throat

Head Examination of the head may show obvious signs of deformity, such as crepitus or bony step-offs in the setting of a skull fracture. Other signs suggestive of basilar skull fracture that should be specifically evaluated are bilateral orbital ecchymosis (Raccoon Eyes) and postauricular bruising (Battle's sign).

Eyes Miosis is commonly seen in opioid and clonidine toxicity, and may also be seen in the setting of pontine hemorrhage. Mydriasis is common in poisoning with compounds with anticholinergic properties (eg, tricyclic antidepressants) and MDMA. Horizontal nystagmus is common in ethanol intoxication and with toxicity from antiepileptic drugs. Vertical nystagmus is uncommon and suggests dissociative agents (eg, phencyclidine and ketamine) or brainstem dysfunction. Gaze deviation may be in response to an ipsilateral hemispheric lesion, a contralateral pontine lesion, or a seizure focus. Roving eye movements do not specifically localize a lesion but suggest that the brainstem is intact. When ice water irrigation of the ear is performed in normal patients, there is tonic deviation of the eyes toward the side of the irrigation followed by rapid nystagmus away from the side of the irrigation. Loss of the former suggests a midbrain or pontine lesion, loss of the latter suggests a cortical lesion, and loss of neither suggests psychogenic coma.

Ears Hemotympanum may be seen in approximately 50% of basilar skull fractures.⁶⁶

Throat Dry mucous membranes are suggestive of profound dehydration or anticholinergic toxicity, whereas increased salivation may be seen with ketamine toxicity.

Skin

Excessively dry skin suggests poisoning with a drug with anticholinergic properties, such as tricyclic antidepressants. Diaphoresis may be seen in any hyperadrenergic state. Coma bullae are classically associated with barbiturate toxicity but may also be seen in other settings, such as infection.⁶⁷ Small linear areas of pinprick-size trauma over veins (track marks) suggest the ongoing abuse of intravenous drugs, particularly opioids, but cannot be used in and of themselves to diagnose the cause of a comatose state.

Bowel Sounds

Markedly decreased bowel sounds are associated with both anticholinergic toxicity and opioid toxicity.

The Toxidrome-Oriented Physical Examination

Syndromes are a constellation of signs or symptoms that together suggest a certain disease entity. In humans, certain toxins or classes of toxins produce stereotypical physical examination findings. These toxic syndromes, or toxidromes, can provide invaluable information. In comatose patients, the use of vital signs and examination of the eye, throat (mucous membranes), skin, and bowel sounds may yield a pattern that strongly suggests a given class of toxins ([Table 2](#)).

IMAGING AND LABORATORY TESTING

Although a thorough history and physical examination will often generate a refined differential diagnosis, imaging studies and laboratory testing play an important role in the diagnosis of coma. Such interventions, however, should serve to refine clinical impressions and should not be ordered indiscriminately as a substitute for thoughtful patient evaluation.

When coma is obviously caused by diffuse neuronal dysfunction, such as hypoglycemia or a known ingestion, CT is rarely if ever necessary. The diagnostic yield of CT in this setting is exceedingly low.⁶⁸ When a structural cause is suspected, particularly in the setting of trauma, CT of the head is essential and will often identify the lesion. In the emergency department, most patients with a structural cause of coma will have a hemorrhagic syndrome.

MRI scans allow greater definition of cortical and subcortical structures and may show cortical injury, laminar necrosis, or white matter disease that is not apparent on a CT scan. Magnetic resonance angiography allows for excellent visualization of the arterial system and is the preferred method for visualization of suspected acute basilar artery occlusion; however, this may not be possible at all institutions. In such instances, CT angiogram or conventional angiography can allow for rapid visualization of the arterial system. The major drawbacks of MRI scans include accessibility, cost, and time necessary to complete the scan.

The authors believe that basic laboratory testing should include the following at a minimum: a complete blood count, to assess for leukocytosis as corroborating evidence of infection and to assess the numerical adequacy of platelets in the event of CNS hemorrhage; an electrocardiogram, to exclude toxin-induced conduction system abnormalities; serum glucose, preferably via a rapid bedside test; serum electrolytes,

| Finding | Opiates | Sedative-Hypnotic Agents | Dissociative Agents |
|------------------|---------------------|---------------------------------|----------------------------|
| Pulse | Normal vs decreased | Normal vs decreased | Increased |
| Blood pressure | Normal vs decreased | Normal vs decreased | Increased |
| Respiratory rate | Markedly decreased | Normal vs decreased | Normal |
| Mucous membranes | Normal | Normal | Salivation (ketamine) |
| Eyes | Miosis | Normal | Nystagmus |
| Skin | Normal | Normal | Normal |
| Bowel sounds | Markedly decreased | Normal | Normal |

including calcium; and tests of renal and hepatic function. Additional high-yield testing in the correct clinical setting may include a serum ammonia level as a marker for hepatic encephalopathy, or as a primary hyperammonemic disorder that may occur in the setting of valproic acid treatment.⁶⁹ An arterial or venous blood gas may also be helpful, particularly when poisoning with salicylates, toxic alcohols, or CO is suspected.

The authors discourage the routine use of urine drug screen (UDS) testing, for several reasons. First, such tests do not measure intoxication or toxicity but, instead, the presence of a drug or drug metabolite, meaning that findings on a positive UDS may be coincident with, rather than causative of, coma. Second, UDS tests may show false negative results. For example, not all benzodiazepines react with commonly used commercial benzodiazepine assays.⁷⁰ In such cases, over-reliance on a UDS may cause a clinician to reject a diagnosis that is clinically apparent. Third, UDS tests may generate false-positive results; this is particularly true with the phencyclidine assay, which is often positive in the setting of commonly used medications such as the cough suppressant dextromethorphan.⁷¹ Finally, and perhaps most importantly, studies suggest that UDS testing does not significantly affect clinical decision making.^{72,73}

Electroencephalographic (EEG) testing may be useful in patients who have a history of a seizure disorder, or who have had several seizures before the development of coma, to exclude NCSE. The authors strongly recommend against emergency department EEG testing when an alternative diagnosis is clear, such as a large subdural hematoma, or strongly suspected in the case of patients with clear alcohol intoxication. When EEG is used in the ED, the authors suggest that an abbreviated protocol be used if at all possible.⁷⁴

Lumbar puncture should be performed in any case in which meningitis or encephalitis is suspected. Historical context, such as a close contact with meningitis; symptoms, such as photophobia or neck pain; or physical signs, such as a fever or meningismus, may all suggest a CNS infection. Unfortunately, historical and physical examination findings are neither sensitive nor specific for the diagnosis of CNS infection.⁷⁵ Therefore, the decision to perform a lumbar puncture must be made on a case-by-case basis by the treating physician. Generally, the authors do not advocate for routine lumbar puncture in all comatose patients, particularly in those for whom an alternative diagnosis is established or strongly suspected.

GRADING SYSTEMS

Grading systems allow providers to quickly convey a general sense of the patient's condition. This is particularly important when one provider cannot examine the patient, as may occur in telephone discussions between providers or during emergency medical service communications.

Two major grading systems are used to assess the depths of coma (**Table 3**). The GCS, first described in 1974,⁷⁶ is a 15-point composite score of eye, motor, and verbal responses developed to assess patients with head trauma. The Full Outline of Unresponsiveness (FOUR) score, first described in 2005, is a 16-point scale that assesses eye, motor, brainstem reflexes, and respirations.⁷⁷ Both rely on clinical findings, have high inter-rater reliability,⁷⁸ and can be performed quickly. The FOUR score has a benefit over GCS in that one of three of the GCS criteria is unreliable in intubated patients. The FOUR score is also a better predictor of mortality in critically ill patients.⁷⁹

Table 3
Glasgow coma scale and full outline of unresponsiveness (FOUR) score

| Glasgow Coma Scale | Full Outline of Unresponsiveness Score |
|----------------------------|---|
| Eye Opening Response | Eye response |
| Spontaneously, 4 | Open and tracking or blinking to command, 4 |
| To speech, 3 | Open but not tracking, 3 |
| To pain, 1 | Closed but open to loud voice, 2 |
| Best Verbal Response | Closed but open to pain, 1 |
| Oriented, 5 | Closed with pain, 0 |
| Disoriented, 5 | Motor response |
| Inappropriate words, 4 | Thumbs up, fist or peace sign, 4 |
| Incomprehensible sounds, 3 | Localizes pain, 3 |
| No response, 1 | Flexion response to pain, 2 |
| Best Motor Response | Extension response to pain, 1 |
| Obeys commands, 6 | No response to pain or myoclonic status, 0 |
| Localizes pain, 5 | Brainstem reflexes |
| Withdrawal from pain, 4 | Pupil and corneal reflexes present, 4 |
| Decorticate flexion, 3 | 1 pupil wide and fixed, 3 |
| Decerebrate extension, 2 | Pupil or corneal reflexes absent, 2 |
| No movement, 1 | Pupil and corneal reflexes absent, 1 |
| | Absent pupil, corneal and cough reflex, 0 |
| | Respiration |
| | Not intubated, regular pattern, 4 |
| | Not intubated, Cheyne-Stokes pattern, 3 |
| | Not intubated, irregular breathing, 2 |
| | Breathes above ventilator rate, 1 |
| | Breathes at ventilator rate or apnea, 0 |

Importantly, both systems exist as scales, meaning that coma is rarely a yes or no delineation. Although many investigators define coma as a GCS of less than 8, this cutoff represents an arbitrary choice more than a significant physiologic distinction.

TREATMENT

The ultimate treatment of coma depends on the cause. In general, there are three overarching themes regarding the treatment of coma.

First, coma from structural causes may be catastrophic and untreatable. However, when the cause is treatable, it can be treated surgically or with geographically targeted pharmacologic or mechanical intervention. The authors advocate for the early involvement of neurosurgical specialists for patients with coma from intracranial hemorrhage or hydrocephalus because early intervention can have an extraordinary effect on both mortality and long-term outcomes. Patients with ischemic cerebrovascular disease should be promptly assessed, ideally by a team that includes a neurologist, to assess their candidacy for either intravenous or intra-arterial thrombolysis.

Second, in patients whose coma is a result of a metabolically induced diffuse neuronal dysfunction, treatment involves progress toward homeostasis. In some cases, such as hypoglycemia and respiratory insufficiency, the goal is expeditious normalization of values such as serum glucose or the partial pressure of oxygen or carbon dioxide in the blood. In other cases, such as hypertensive encephalopathy and hyponatremia, the correct initial treatment involves only a partial correction, and an abrupt return to normal could be clinically devastating.⁸⁰

Third, in patients whose coma is a result of a toxin-induced diffuse neuronal dysfunction, the most important intervention, established more than 50 years ago, is

the provision of appropriate supportive care.⁸¹ Initial supportive care includes securing the airway, assuring adequate oxygenation and ventilation, and assuring appropriate circulation with intravenous fluids and, if necessary, vasopressors. Advanced supportive care may include altering systemic or compartmental pH to reduce drug toxicity or increase drug excretion, such as administering sodium bicarbonate for tricyclic antidepressant or salicylate toxicity, or the administration of intravenous lipid emulsion to alter drug distribution.⁸² Although there are specific toxins that induce coma for which specific antidotal therapy may be critical or lifesaving (eg, fomepizole for toxic alcohols, hydroxocobalamin for cyanide, or naloxone for opioids), antidotal therapy plays little or no role in treating most toxins that may produce coma.

SUMMARY

Coma represents a true medical emergency. Although drug intoxications are a leading cause of coma in patients who present to the emergency department, other metabolic disturbances and traumatic brain injury are common causes as well. The general emergency department approach to the patient with coma begins with stabilization of airway, breathing, and circulation, followed by a thorough physical examination to generate a limited differential diagnosis that is then refined by focused testing. Definitive treatment is ultimately disease-specific.

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