Diagnosis of Coma

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KEYWORDS

• Coma • Neurocritical care • Disorders of consciousness

KEY POINTS

- The differential diagnosis for the comatose patient is broad and includes structural abnormality, seizure, encephalitis, metabolic derangements, and toxicologic etiologies.
- Obtaining a good collateral history and physical examination are imperative for identifying the correct diagnosis.
- We discuss the diagnostic testing and treatment considerations for each cause of coma.

INTRODUCTION

Coma may be defined as a state of prolonged unresponsive unconsciousness. As such, it is not a disease process, but rather a symptom that may be caused by a variety of disease processes. Causes include structural, metabolic, toxicologic, and infectious etiologies; prognosis varies substantially with the underlying cause. The common pathway resulting in coma is thought to include disruption of neuronal function or pathways from the ascending reticular activating system through the thalami to the cortex.[1] It is important to note that only lesions affecting the ascending reticular activating system or bilateral hemispheres result in coma and coma should never be attributed to unilateral cortical lesions.

Coma is by definition a medical emergency, because it impairs the patient's ability to protect the airway; many underlying causes of coma are also independently emergent. In a study of *International Classification of Diseases,* 9th edition, codes, coma was responsible for 29 emergency department visits per 100,000 population,[2] a decreasing number that likely represents under-reporting as emergency department workup to identify an underlying cause is improving.

Treatment of coma is targeted toward immediate stabilization, identification in particular of reversible underlying etiologies, and correcting alterations in normal physiologic processes. This article contains a differential diagnosis for coma etiologies, prioritized by acuity and reversibility, along with suggested diagnostic and stabilization strategies. In all cases, information obtainable from the patient will be limited,

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and consequently the initial differential must be formed on the basis of historical information from surrogates and physical examination.

HISTORY AND PHYSICAL EXAMINATION PEARLS

History

The patient's history should provide the majority of information needed to narrow the diagnosis. In addition to knowing the right questions to ask, knowing the order in which to ask them will help to triage the patient and to formulate a plan at the same time. In some cases collateral information will be unavailable resulting in reliance solely on physical examination and ancillary testing.

- Acuity and onset
  - Was the change sudden?
  - Was the patient showing earlier signs such as excessive sleepiness, confusion, or memory problems before coma onset?
  - Was the patient experiencing other symptoms such as fevers, unusual movements, weakness, numbness or tingling, headaches, light sensitivity, or neck or back pain?
  - What was the patient doing when this occurred?
  - When was the last time seen in their usual state of health?
- History of brain surgery?
- Vascular risk factors
  - Hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, smoking history, obstructive sleep apnea, atrial fibrillation, history of stroke or intracerebral hemorrhage, family history of aneurysms, or history of thrombosis or thromboembolism?
- Seizure risk factors
  - Personal or family history of seizures or status epilepticus?
  - Febrile seizures as a child?
  - History of head trauma with loss of consciousness?
  - History of central nervous system infection?
- History of psychiatric disease?
  - History of depression or suicidal ideations?
  - Prescribed psychiatric medications?
  - Compliant with medications?
  - When was the last refill and how much is left?
- History of substance abuse?
  - Which substances?
  - How much?
  - Use of injectable drugs?

Physical Examination

Vital signs

Tachycardia is nonspecific and may reflect hemodynamic compromise. The patient may have an elevated heart rate owing to pain, seizure, or intoxication with an adrenergic or anticholinergic substance. Rapid atrial fibrillation may be reactive but should raise concern for ischemic stroke as the cause of altered sensorium.

Bradycardia may result in cerebral hypoperfusion when associated with relative hypotension. Additionally, particularly when seen in conjunction with hypertension and decreased or irregular breathing, known as Cushing's triad, it may signify elevated intracranial pressure.

Hypertension, similarly, may directly cause encephalopathy and thus leads to a diagnosis of hypertensive emergency. However, hypertensive encephalopathy is usually relatively mild and the diagnosis should be reached only after excluding other acute processes. In acute brain injury blood pressure is augmented by the brain's intrinsic autoregulatory mechanism to maintain cerebral blood flow. Hypertension can also be seen in patients with seizures or those with ingestion of adrenergic or anticholinergic substances.

Hypotension may result in cerebral hypoperfusion and coma. It is otherwise a nonspecific finding with a broad differential diagnosis, including various forms of end-organ dysfunction such as shock, end-stage kidney disease, or end-stage liver disease. It may also be seen in the setting of opiate, barbiturate or benzodiazepine intoxication, overdose of antihypertensive medication, or loss of sympathetic tone from a spinal cord injury.

Tachypnea may be a central phenomenon known as central neurogenic hyperventilation, occurring in response to a lesion in the midbrain or diencephalon. However, tachypnea is more frequently a result of a primary pulmonary process, a pain response, or as compensation for a metabolic acidosis as seen in sepsis and drug intoxication (Kussmaul's breathing).

Apnea or irregular breathing patterns, when central in origin, have multiple variants including:

- Cheyne–Stokes respirations: Periods of "crescendo–decrescendo" tachypnea with periods of apnea, which can be seen in metabolic encephalopathy, supratentorial lesions, and lesions of the midbrain or diencephalon.
- Apneustic: Prolonged inspiration and expiration separated by periods of apnea, which can be seen in pontine lesions.
- Ataxic (Biot's): Periods of tachypnea and apnea lacking the crescendo–decrescendo quality of Cheyne–Stokes respirations and is associated with lesions in the medulla. This breathing pattern usually carries a poor prognosis.

Additional examination findings

Hiccups may be seen with medullary lesions. Additionally, outside of gastrointestinal disease, vomiting may be indicative of hydrocephalus with increased pressure to the area postrema located on the floor of the fourth ventricle.

Head, Eyes, Ears, Nose, and Throat

Fundoscopic examination may show papilledema suggestive of elevated intracranial pressure. Presence of retinal hemorrhage or detachment is suggestive of head trauma. Periorbital ecchymosis ("raccoon eyes"), mastoid ecchymoses ("Battle's sign"), and hemotympanum are concerning for basal skull fracture. Dry mucosal membranes may be a result of dehydration or intoxication with antidepressants, anticholinergics, neuroleptics, antihistamines, muscle relaxants, seizure medications, or antihypertensives. Conversely, excessive salivation, lacrimation, and diaphoresis can point to cholinergic intoxication. Finally, scleral icterus may be a sign of end-stage liver disease or hepatic encephalopathy with or without cerebral edema.

Neurologic Examination

Pupils

Anisocoria is present in the general population and may be a benign finding, especially if reactivity is intact. A unilateral dilated and nonreactive pupil may suggest uncal herniation with compression of cranial nerve III, or a midbrain lesion affecting the third

nerve nucleus. Abnormal pupillary constriction or dilation can be caused by medications with adrenergic or cholinergic effects. When accompanying coma, miotic ("pinpoint") pupils most commonly indicate intoxication with opiates or benzodiazepines, cholinergic substances such as organophosphates, or a structural lesion in the pons. Bilateral dilated pupils with decreased or absent pupillary constriction may be indicative of a severe diffuse cerebral process; however, this finding can also be found in profound intoxication, sedation, or hypothermia (**Table 1**).

Extraocular motion

Vestibulo-ocular reflex Loss of this reflex suggests an abnormality in the brain stem or higher cortical function, but is nonspecific in etiology. This condition can be assessed with oculocephalic maneuver or cold caloric testing. Forced gaze deviation or gaze preference involves functional disruption for the frontal eye fields. The patient will gaze toward the side of stroke or away from the seizure focus. Dysconjugate gaze is generally nonspecific for diagnostic purposes, although skew deviation is a vertical misalignment of the eyes and is a sign of a brain stem or cerebellar lesion. Although unilateral nystagmus may be seen in peripheral vestibular disease, when it is bidirectional, vertical or rotatory, and nonfatiguing, it is indicative of a cerebellar or brain stem lesion or substance intoxication such as phencyclidine. A downward fixed gaze, also known as "setting sun sign," is caused by a midbrain lesion (Parinaud syndrome). Ocular bobbing is associated with pontine lesions.

Other cranial nerve findings

Absence of the corneal, cough, or gag reflexes is another sign of severe diffuse cerebral dysfunction, but the etiology is nonspecific. Central facial asymmetry, in which eyebrow raise is preserved, is seen with cortical or subcortical injury. Head version may be indicative of a focal seizure originating from the contralateral hemisphere.

Motor and sensory findings

In comatose patients, the sensory portion of the neurologic examination is limited to their response to stimulation, which is performed during the motor examination. Increased tone or rigidity can indicate serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, subacute or chronic brain injury, seizure, or chronic spinal cord injury. Spontaneous and purposeful movement is often times a reassuring finding. Response to noxious stimulation in the upper extremities can be categorized as either localization, withdrawal, decorticate, or decerebrate posturing. Response to noxious stimulation in the lower extremities can be categorized as either spontaneous, withdrawal, or triple flexion. Triple flexion is a nonsustained, stereotyped flexion at the hip, knee, and ankle and is a brain stem–mediated response reflecting a loss of cortical involvement. Absence of motor responses is nonspecific and could indicate organic disease or other severe metabolic disease or intoxication.

Reflex testing

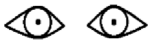
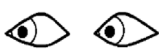
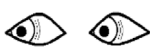
Hyperreflexia or clonus may be seen as part of serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia or tetanus. Hyporeflexia may be seen in acute brain or spinal cord injury or a neuromuscular process such as botulism.

DIFFERENTIAL DIAGNOSIS

Structural Causes

It is critical in patients with undifferentiated coma to exclude structural causes, because they form some of the most acute and in many cases very treatable causes of coma. Broadly speaking, structural causes of coma can be grouped into vascular

Table 1
Abnormal eye findings and causes

Bilateral miosis "pinpoint pupils" 	Opiates Benzodiazepines Barbiturates Cholinomimetic substances (pilocarpine, carbachol, etc.) Cholinesterase inhibiters (neostigmine, organophosphates, etc) Clonidine Phenothiazine Ergot derivatives Pontine lesion
Bilateral mydriasis 	Anticholinergics (atropine, diphenhydramine, scopolamine) Sympathomimetics (cocaine, methamphetamines, MDMA, dopamine, phenylephrine, norepinephrine) Serotonergics (selective serotonin reuptake inhibitors, psilocybin, d-lysergic acid diethylamide, dextromethorphan) Opioid or benzodiazepine withdrawal Oxytocin Increased intracranial pressure with bilateral cranial nerve III compression (nonreactive) Botulinum toxin Post-traumatic iridoplegia Diabetic neuropathy
Anisocoria 	May be a normal finding, especially if minimal difference in size and both reactive Unilateral cranial nerve III compression (herniation) Midbrain lesion affecting the cranial nerve III nucleus Posterior communicating artery aneurysm Horner's syndrome Adie's tonic pupil Post-traumatic irido plegia Diabetic neuropathy
Conjugate gaze deviation 	Structural lesion involving the frontal lobe ipsilateral to direction of gaze Rarely, can be caused by pontine lesion Seizure involving the frontal lobe contralateral to direction of gaze
Skew 	Brain stem or cerebellar lesion
Nystagmus 	Bidirectional and sustained, vertical or rotatory - brain stem or cerebellar lesion
Sunset Sign 	Loss of vertical gaze - dorsal midbrain lesion or hydrocephalus
Ocular bobbing 	Extensive pontine lesion, associated with poor prognosis

lesions, space-occupying lesions, and lesions causing diffusely elevated intracranial pressure through cerebrospinal fluid outflow obstruction. Some lesions may span multiple categories, such as a space-occupying intracranial hemorrhage owing to a ruptured arteriovenous malformation.

All patients presenting with coma should undergo an emergent head computed tomography (CT) scan to exclude space-occupying structural lesions and hydrocephalus; this is especially true for those with focal neurologic deficits, such as cranial nerve findings. The decision to perform neuroimaging must be made on clinical grounds and not delayed for results of laboratory testing, because many identifiable structural causes require time-critical treatment.

Comatose patients will have a decreased intrinsic ability to maintain their airway, and most will require intubation to ensure safety for neuroimaging. Any with overt evidence of elevated intracranial pressure such as a herniation syndrome warrant empiric osmotic therapy before neuroimaging, especially since this imaging requires prolonged supine positioning.

The identification of a discrete space-occupying lesion will usually require specialist consultation, because classification into operative versus nonoperative lesions is beyond the scope of most emergency medicine practitioners. Any lesion causing substantial mass effect, herniation, or suspicion for globally elevated intracranial pressure should be treated with osmotic therapy such as mannitol or hypertonic saline while awaiting neurosurgical consultation. If this situation requires central line placement, the subclavian site is preferred to limit potential obstructions of cerebral venous outflow. Steroid administration should be reserved for vasogenic edema owing to underlying tumor and is not recommended for edema surrounding hemorrhages.[3,4] Hydrocephalus severe enough to result in coma, particularly if caused by intraventricular hemorrhage or cerebrospinal fluid outflow obstruction, will likely require emergent endoventricular drain placement by neurosurgery. It should be mentioned that procedural management of infratentorial lesions is controversial and may include either endoventricular drain or suboccipital decompression at the discretion of the neurosurgical team.

If an intracranial hemorrhage is diagnosed, reversal of anticoagulation is recommended. Reversal of antiplatelet agents for intraparenchymal hemorrhages has been shown to double the risk of death or dependency[5] and has therefore been removed as a routine practice recommendation.[5] This development does not mean to imply that specific individual patients (such as those with active arterial bleeding or undergoing neurosurgical procedures) may not derive some benefit. A cornerstone of management of intracranial hemorrhage is careful management of blood pressure. A goal of systolic blood pressure is controversial, although targeting to less than 160 has been shown to decrease hematoma expansion without significant repercussions to renal function.[6,7] There is no evidence for the use of prophylactic antiepileptic drugs. Last, in patients with intracranial hemorrhage identified on noncontrast CT scan, CT angiography may identify a responsible neurovascular lesion warranting intervention.

Neurovascular etiologies of coma warrant specific discussion owing to their time-sensitive and treatable nature. Basilar system thrombosis carries an extremely poor untreated prognosis, and in the neurointerventional era has time-critical and potentially effective treatments. The sensitivity of a noncontrast head CT scan for basilar thrombosis has been reported to be as high as 50% to 70%[8,9] with high clinical pretest probability and when reviewed by expert neuroradiologists. In many clinical scenarios even this moderate sensitivity will not be achievable, and consequently CT angiography is increasingly becoming a standard diagnostic evaluation for comatose

patients and especially those with cranial nerve findings. Identifying acute basilar clot has significant impact on outcomes, with 45% to 46%[10,11] of those treated via endovascular therapy having good outcomes (modified Rankin Scale of 0–2, functional independence) versus an untreated historical norm of approximately 10%.

In some cases, pontine injury may cause locked-in syndrome, which can be difficult to differentiate from coma. In this syndrome, motor function is impaired but sensory function and consciousness are preserved; patients may be able to use their eyes to communicate and have variably preserved cranial nerve function depending on the exact level of the lesion. Careful attention to cranial nerve and particularly the oculomotor components of the examination will ensure that locked-in syndrome is not mistaken for coma. Although most strokes causing acute coma are basilar in nature, there are uncommon supratentorial causes as well. These by necessity must be bilateral, and may include strokes affecting multiple territories. Possible etiologies include cardioembolic strokes as well as strokes arising from the artery of Percheron, which is an anatomic variant in which the arterial supply of the bilateral paramedian thalami arises unilaterally.

Depending on local institutional practices and resources, MRI may be considered in the evaluation of structural causes of coma. This modality may be particularly helpful in identifying brain stem pathology, including early infarction in the absence of overt large vessel occlusion, as well as diffuse axonal injury from traumatic brain injury. In most cases, this determination will not result in an immediate treatment change and so may be deferred in many institutions; however, early identification of brain stem infarct may obviate a comprehensive search for other etiologies, inform code status discussions, and change disposition (ie, medical intensive care unit for undifferentiated coma vs neurologic intensive care unit for infarct vs trauma or neurotrauma intensive care unit for diffuse axonal injury or traumatic brain injury) (**Table 2**).

Nonconvulsive Status Epilepticus Versus Postictal State

Status epilepticus is defined as at least 5 minutes of clinical or electrographic seizure activity, or multiple seizures without a return to neurologic baseline. Status epilepticus is further divided into convulsive or nonconvulsive. Generalized convulsive status epilepticus is characterized by tonic or tonic–clonic movements accompanied by an altered mental status. In contrast, nonconvulsive status epilepticus does not have obvious signs suggesting prolonged seizures, but rather is defined electrographically. Patients with nonconvulsive status epilepticus may have subtle signs of seizures such as facial or extremity twitching, eye deviation or nystagmus, or it may manifest only as an abnormal mental status. Alternatively, the patient may present with agitation, aphasia, staring, confusion or coma.

Uncontrolled generalized convulsive status epilepticus may transition into nonconvulsive status epilepticus; therefore, timely recognition and treatment are essential.

Table 2
Structural causes of Coma

Ischemic	Hemorrhagic	Other
Bilateral anterior cerebral artery strokes	Subarachnoid hemorrhage	Traumatic brain injury
Basilar occlusion	Thalamic hemorrhage	Hydrocephalus
Vasculitis	Pontine hemorrhage	Midbrain tumor
		Central pontine myelinolysis
		Supratentorial mass causing herniation
		Multiple sclerosis

Patients who present with nonconvulsive status epilepticus usually have underlying comorbidities and are acutely ill. The differential of the inciting disease is broad and includes toxic or metabolic derangements, infection, or structural brain lesions. Nonconvulsive status epilepticus is also generally more refractory to treatment.[12]

Diagnostic testing

A noncontrast CT scan of the head is standard of care to rule out acute structural etiologies. MRI of the brain with and without contrast can be considered once the patient has been stabilized.

An electroencephalogram (EEG) is the only definitive method of making the diagnosis of nonconvulsive status epilepticus, and to differentiate nonconvulsive status epilepticus from postictal state. Continuous EEG monitoring is preferred over routine EEG. The duration of EEG monitoring is uncertain; however, for patients who have risk factors for developing status epilepticus, 24 hours of monitoring should be considered.[13]

Laboratory testing should include glucose, basic metabolic panel, complete blood count, lactate, and creatine kinase levels, which may be elevated in prolonged seizure. Serum prolactin level is nonspecific for the diagnosis of status epilepticus; however, it may be useful in differentiating patients with epileptic seizures from those with psychogenic nonepileptic seizures if drawn at most 20 minutes from the time of seizure.[14] Antiepileptic drug levels should be obtained when appropriate.

A lumbar puncture may be of value to acutely exclude central nervous system infection. It may also allow for testing of infrequent causes, such as autoimmune encephalitis or occult malignancy when the etiology is uncertain. If a lumbar puncture is performed in the setting of suspected or confirmed status epilepticus additional cerebrospinal fluid should be banked to facilitate possible specialized testing.

Treatment

After initial stabilization and airway attainment, targeted therapy includes the following. Benzodiazepines are the first-line treatment for status epilepticus. Intravenous (IV) or intramuscular lorazepam or midazolam are preferred for their favorable pharmacodynamics. Lorazepam should be dosed at 0.1 mg/kg, divided into multiple doses to attenuate subsequent hypotension and respiratory depression. Similarly, midazolam should be dosed at 0.2 mg/kg.

Concurrently, the patient should receive an antiepileptic drug, including:

- Levetiracetam 1000 to 3000 mg
  - Minimal side effects
- Lacosamide 200 to 400 mg
  - Minimal side effects
- Phenytoin 20 mg/kg load, may repeat 5 to 10 mg/kg dose in 10 minutes
  - Phenytoin load may result in arrhythmias or hypotension; for this reason fosphenytoin is preferred
- Valproate 20 to 40 mg/kg
  - Side effects include hepatotoxicity, thrombocytopenia, and pancreatitis
- Phenobarbital 15 to 20 mg/kg
  - Side effects include hypotension and respiratory depression

If the patient continues to seize despite appropriate benzodiazepine dosing and at least one antiepileptic drug, they are defined as having refractory status epilepticus. A continuous infusion should be initiated and titrated to seizure suppression on EEG.

- Propofol: Load with a 1 to 2 mg/kg bolus followed by infusion starting at 20 μg/kg/min.

- Side effects include hypotension, respiratory depression, and propofol infusion syndrome including metabolic acidosis, rhabdomyolysis, cardiac and renal failure.
- Midazolam: 0.2 mg/kg dose followed by infusion starting at 0.05 to 2 mg/kg/h.
  - Side effects include hypotension and respiratory depression.
- Pentobarbital: 5 to 15 mg/kg loading dose followed by continuous infusion at 0.5 to 5 mg/kg/h, at a maximum rate of 50 mg/min.
  - Side effects include hypotension, cardiac depression, respiratory depression, and ileus.

The choice for preferred antiepileptic drug administration is a topic of debate, although IV administration is vital for urgent seizure control. Traditionally phenytoin, valproate, and phenobarbital were considered the agents of choice[15] and were selected based on their side effect profile and ease of administration. Newer agents including levetiracetam, brivaracetam and lacosamide have since gained popularity owing to their relatively lower incidence of side effects. A recent randomized clinical trial[16] was stopped early for futility and showed that levetiracetam was as efficacious as phenytoin and valproate in aborting status epilepticus. Despite the excellent tolerability of brivaracetam and lacosamide, there is currently a paucity of strong evidence to support their use in standard of care.

Encephalitis

Meningoencephalitis must be considered when a patient presents in a comatose state. Both infectious and noninfectious etiologies should be reviewed and additional history obtained to narrow the scope of treatment. Meningitis on its own does not manifest with an altered mental status and presents instead with meningismus: headache, neck stiffness, and photosensitivity. Encephalitis, in contrast, affects the brain focally or diffusely and may present with a myriad of signs, including confusion, lethargy, personality changes, motor or sensory deficits, or seizures. Cerebritis describes regionalized inflammation of the brain and is associated with infectious etiologies. Immunosuppressed patients may have primary or coinfections with rare or atypical diseases. Aseptic meningitis may include drug-induced, postinfectious or paraneoplastic etiologies (**Table 3**).

Diagnostic testing

A CT scan of the head may not be abnormal in meningitis or encephalitis, but may have a localized area of hypodensity reflecting vasogenic edema surrounding an abscess. It is also necessary to exclude a mass lesion to ensure safe lumbar puncture. An MRI of the brain with and without contrast may be considered once the patient has been treated empirically for potential reversible causes.

Routine serum laboratory tests may reveal a leukocytosis and lactic acidosis.

Lumbar puncture must be performed in a timely manner to isolate the offending agent. Cerebrospinal fluid findings and their significance are listed in **Table 4**. Basic cerebrospinal fluid studies include glucose, protein, cell count with differential, herpes simplex virus polymerase chain reaction, varicella zoster virus polymerase chain reaction and antibodies, cytomegalovirus polymerase chain reaction, Epstein–Barr virus polymerase chain reaction, and bacterial culture. Opening pressure is important because it can be suggestive of a specific underlying process. Additional studies may be sent if atypical or rare infections are considered, or if there is concern for autoimmune encephalitis.

An EEG should be performed to exclude nonconvulsive status epilepticus in comatose patients with evidence of central nervous system infection (see **Table 4**).

Table 3
Causes of Meningoencephalitis

Bacterial	Viral	Fungal	Parasitic	Autoimmune	Drug Induced	Other
Borrelia species	Herpes simplex	*Aspergillus* species	*Acanthamoeba* species	Anti-AMPA	Allopurinol	Acute Disseminated Encephalomyelitis
Escherichia coli	Varicella zoster	*Blastomyces dermatitidis*	*Balamuthia mandrillaris*	Anti-Ampithysin	Azathioprine	Carcinomatous meningitis
Group B Streptococcus	Cytomegalovirus	*Candida* species	*Naegleria fowleri*	Anti-ANGA	Carbamezepine	Central nervous system vasculitis
Haemophilus influenzae	Epstein-Barr virus	*Cocciodes immitis*	*Taenia solium*	Anti-ANNA	Cephalosporins	Creutzfeldt–Jakob disease
Klebsiella species	Human herpes virus-6	*Cryptococcus* species	*Toxoplasma gondii*	Anti-CASPR2	Ciprofloxacin	Fabry disease
Leptospira species	Coxackie	*Histoplasma capsulatum*	*Trypanosoma brucei*	Anti-CRMP	Intrathecal chemotherapy agents	Incomplete treatment of previous infection
Listeria monocytogenes	Echovirus			Anti-DPPX	Isoniazid	Lymphoma
Mycobacterium tuberculosis	Human enteroviruses			Anti-GABA	Intravenous immunoglobulin	Neurosarcoidosis
Mycoplasma pneumoniae	Rotavirus			Anti-GAD65	Lamotrigine	Progressive multifocal Leukoencephalopathy
Neisseria meningitidis	Adenovirus			Anti-GFAP	Metronidazole	
Rickettsia species	Respiratory syncytial virus			Anti-LGI1	Nnonsteroidal anti-inflammatory drugs	
Staphylococcus aureus	Rhinovirus			Anti-mGluR1	Penicillins	
Streptoccocus pneumoniae	Influenza A and B			Anti-NMDA	Pyrazinamide	
Treponemia pallidum	Parainfluenza viruses			Anti-PCA	Pyridium	
	Human immunodeficiency virus			Striated muscle antibody	Sulfasalazine	
	Powassan virus				Trimethoprim–sulfamethoxazole	
	Colorado tick fever virus					

Western equine encephalitis
Venezuelan equine encephalitis
St. Louis encephalitis
Eastern equine encephalitis
California encephalitis virus
La Crosse encephalitis
West Nile virus
Human T-cell lymphotropic virus 1 and 2
Parvovirus
Hepatitis A and B virus
Lymphocytic choriomeningitis
Rabies virus
Measles
Mumps
Rubella

Table 4
Toxicologic causes of Coma

Environmental	Drugs	Metabolic
Carbon monoxide poisoning	Alcohol	Hypoglycemia
Hypothermia	Benzodiazepines	Hyperglycemia/diabetic ketoacidosis
Organophosphate poisoning	Barbiturates	Uremia
	Opiates	Hepatic encephaopathy
	Anticholinergics	Hypercalcemia
	Toxic alcohols	Hypocalcemia
		Myxedema coma
		Hypercapneic respiratory failure
		Wernicke's encephalopathy

Treatment

If there is suspicion for infectious cause, steroids and empiric antimicrobial medication should be started without delay. For streptococcal meningitis, steroids have been shown to reduce mortality if given before or with the initial dose of antibiotics.[17]

The recommended empiric regimen includes:

- Dexamethasone 0.15 mg/kg every 6 hours for 2 to 4 days
- Vancomycin: 15 to 20 mg/kg every 8 to 12 hours
- Third generation cephalosporin:– for example, ceftriaxone 2 g every 12 hours
- Acyclovir 10 mg/kg every 8 hours
- If the patient is more than 50 years old or immunosuppressed, ampicillin should be added for coverage of atypical organisms
- If the patient has had a recent neurosurgical procedure, a fourth-generation cephalosporin such as cefepime should replace the third-generation cephalosporin

Fever should be treated to avoid secondary brain injury. Prophylaxis with antiseizure medication is not recommended unless the patient has clinical or electrographic seizures. Autoimmune encephalitides are treated acutely with high dose steroids (methylprednisolone 1 g/d for 5 days), intravenous immunoglobulin (2 g/kg divided over 5 days) or plasma exchange. Steroid-sparing agents may be considered if there is a good clinical response to acute treatment.

Toxicologic Causes

Because coma may be caused by numerous toxins and laboratory identification of them is time consuming and at times misleading (eg, having limited ability to differentiate acute drug toxicity from recent ingestion), an initial differential diagnosis must be formed and empiric therapy begun based solely on history and physical examination, with urine toxicologic screens and other laboratory testing serving primarily purposes of confirmation and assisting in longitudinal care. The more common, time-sensitive, and treatable toxicologic causes of coma are discussed in detail elsewhere in this article. A wide range of uncommon toxins exist and require supportive care while seeking expert consultation (**Table 5**).

One of the most common and most immediately reversible etiologies is opiate toxicity, in which case coma is usually accompanied by miosis and decreased respiratory drive. Although most frequent in recreational drug users, iatrogenic opiate toxicity, for example, among elderly patients with fluctuating renal function, should also be considered. Clinicians should have a low threshold for administration of

Table 5
Cerebrospinal fluid findings

	Opening Pressure (cmH_2O)	Glucose (mg/dL)	Protein (mg/dL)	White Blood Cell Count	Differential
Normal	5–20	>50 or 2/3 serum glucose	<50	<5	No differential
Bacterial	Elevated	<50	elevated	>500	Neutrophilic predominance
Viral	Normal	Normal	Normal or slightly elevated	<1000	Lymphocytic predominance
Fungal or tuberculosis	Elevated	Normal or low	Elevated	<1000	Lymphocytic predominance
Autoimmune	Normal	Normal	Elevated	<500	Lymphocytic predominance

naloxone, a competitive opiate antagonist, because it has a benign side effect profile and may help to avoid intubation. It should be noted that meperidine and propoxyphene result in mydriasis; naloxone administration should not be withheld solely on the basis of this physical examination finding. Last, naloxone has a short half-life, often shorter than that of the opiate itself, and especially in the context of an unknown opiate ingestion patients must be monitored for recurrence of toxicity as the naloxone is metabolized.

Benzodiazepines are another medication class with substantial potential to cause coma, particularly in intentional/suicidal ingestions. Benzodiazepines taken in isolation are rarely fatal and there are no pathognomonic physical examination findings[18]; suspicion must be based on historical clues. The main physical examination finding consistent with benzodiazepine toxicity is depressed mental status, which may be as severe as complete electroencephalographic silence on EEG. Compromised respirations are possible but much less common than with opiate or barbiturate ingestions. Flumazenil is a competitive antagonist that can be used to reverse cases of known acute-only benzodiazepine toxicity, but should be avoided in cases of unknown or chronic benzodiazepine administration to avoid precipitating potentially life-threatening withdrawal and intractable seizures. Care in such cases is primarily supportive while awaiting toxin metabolism.

Barbiturate ingestion presents similarly to benzodiazepine toxicity but with more pronounced respiratory and cardiovascular suppression; no specific reversal agent is available and care is supportive including mechanical ventilation and vasopressor support.

Acute alcohol intoxication may result in coma when blood levels exceed 0.3%; approximately 1% of all alcohol intoxication visits require critical care,[19] which is generally supportive and may include management of accompanying bradycardia and hypotension. Rapid testing of exhaled breath levels or blood levels is commonly available and may assist with risk stratification and disposition decisions. Rapid testing for toxic alcohols such as methanol, ethylene glycol, and isopropyl alcohol is largely unavailable; elevated osmolar gap and anion gap metabolic acidosis (in the cases of methanol and ethylene glycol) should raise clinical suspicion. When clinical suspicion exists, empiric administration of fomepizole, an alcohol dehydrogenase

inhibitor preventing breakdown to toxic metabolites, should be initiated while awaiting confirmatory testing. Last, Wernicke encephalopathy has been reported to cause reversible coma[20,21] and thiamine should be administered empirically to comatose patients with suspicion of alcohol use disorders.

Severe carbon monoxide poisoning may also result in coma; again there are no pathognomonic findings and high clinical suspicion must be maintained. Although more common in the winter owing to higher home heating needs, 30% carbon monoxide poisoning is intentional[22] and may therefore occur at all times of the year. Diagnosis is supported by pulse co-oximetry or laboratory spectrophotometry, but owing to poisoning of the oxidative phosphorylation pathway symptoms may persist after blood carbon monoxide levels have returned to baseline. As a result, normal level should not be used to exclude toxicity in an appropriate clinical context. When available and performed from the emergency department, MRI showing restricted diffusion specifically in the region of the globus pallidus is strongly supportive of carbon monoxide poisoning. Aside from supportive care, specific treatment includes oxygen supplementation and consideration of hyperbaric oxygen therapy.

Metabolic Causes

Hypoglycemia is one of the most common and most immediately reversible causes of coma. Any patient presenting with coma should either have a fingerstick glucose checked or empiric administration of dextrose (preceded by thiamine if the clinical context suggests concurrent alcohol abuse). Patients who are chronically hyperglycemic may become symptomatic even with low-normal glucose levels. An underlying explanation for hypoglycemia such as insulin overdose should always be sought; in the case of accidental overdose of short-acting insulin, emergency department observation and discharge may be all that is indicated, whereas patients with intentional overdoses, overdoses of long-acting insulin, and unexplained hypoglycemia should be admitted for more prolonged monitoring and further workup.

Hypercarbic respiratory insufficiency also frequently leads to depressed mental status and coma. At times patients may present with clinically evidence hypoventilation as a cause; pulmonary disease such as chronic obstructive pulmonary disease may also play a less overt role. Given that venous carbon dioxide cannot be lower than arterial carbon dioxide, a normal venous blood gas is sufficient to exclude clinically significant hypercarbia. If the venous carbon dioxide is elevated an arterial blood gas should generally be performed to confirm this finding. Although depressed mental status is a contraindication to unsupervised biphasic positive airway pressure, cases of hypercarbia attributed to neuromuscular disease or respiratory muscle fatigue may benefit from a short-term (20–30 minutes) trial of biphasic positive airway pressure under direct observation to determine if improved carbon dioxide clearance will result in a mental status suitable for longer term biphasic positive airway pressure. Worsening hypercarbia or failure of mental status changes to resolve should prompt intubation. As opposed to neuromuscular causes, cases of central hypoventilation will generally not respond to biphasic positive airway pressure and mechanical ventilation will be required. Once hypercarbia has been resolved, patients should be reevaluated to exclude additional contributors to coma (eg, opiate administration leading to hypercarbia).

When severe, numerous electrolyte abnormalities may result in coma. Routine laboratory evaluation should include serum electrolytes, including calcium and magnesium levels. Correction of identified abnormalities should be initiated in the

emergency department before admission; most patients will likely require inpatient management. Evaluation for underlying causes of electrolyte abnormalities can generally be deferred to the inpatient setting. Last, although usually obvious from historical or environmental clues, hypothermia may also result in coma and it should be ensured that all comatose patients have a core temperature documented as part of their initial evaluation.

Hepatic Encephalopathy

Any patient with history or clinical examination stigmata (such as jaundice or spider telangiectasias) of liver disease presenting with coma should have an ammonia level checked to determine if hepatic encephalopathy may be responsible. The pathogenesis of hepatic encephalopathy is incompletely understood and the degree of hyperammonemia does not directly correlate with degree of encephalopathy. Consequently, for those with any ammonia elevation, treatment with lactulose should be initiated and continued until clinical resolution of symptoms; rifaximin may be a useful adjunct and is thought to decrease intestinal bacterial ammonia production. Contributing conditions such as upper gastrointestinal tract bleeding should be identified and corrected. Administration of flumazenil may be considered because it has been shown to improve symptoms of hepatic encephalopathy, even in the absence of benzodiazepine use; however, this effect may often be transient and no statistically significant effect on mortality has been demonstrated.[23]

Endocrine

Thyroid dysfunction in the form of severe decompensated hypothyroidism can result in an entity termed “myxedema coma.” This syndrome includes hypoactive delirium or coma, hypoventilation, bradycardia, hypotension, hypothermia, thick coarse skin, and thinning hair. Seizures may occur as well, especially in the setting of severe metabolic derangements. It is important to also investigate precipitating factors such as infection, cold exposure, and recent trauma. An association exists between decompensated hypothyroidism and intoxication with opioids or other classes of sedating medications, as well as with amiodarone use.

Diagnostic testing

The mainstay of diagnosis is confirmatory thyroid function tests: serum thyroid-stimulating hormone (elevated in primary hypothyroidism but reduced in secondary hypothyroidism), free thyroxine (reduced). Cortisol is often decreased as a result of either primary or secondary adrenal insufficiency and in this case cosyntropin stimulation test may be helpful. Hypoglycemia may result from decreased gluconeogenesis and adrenal insufficiency. Hyponatremia is usually a result of coexisting syndrome of inappropriate diuretic hormone. Elevated creatine kinase and a reduced glomerular filtration rate may be present. Furthermore, hypoxemia and hypercapnia may be seen on blood gas. The electrocardiogram may show sinus arrhythmias and QT prolongation. Therefore, continuous monitoring is recommended. Additionally, EEG monitoring should be performed to exclude nonconvulsive status epilepticus. Lumbar puncture, if performed incidentally, may have an elevated protein but is otherwise diagnostically nonspecific. There are usually no specific abnormalities seen on neuroimaging.

Treatment

Because incidence of myxedema coma is relatively low, there is clinical equipoise as to the exact treatment regimen. Though traditionally a large dose of levothyroxine was the preferred approach, there exist alternative regimens combining tri-iodothyronine and thyroxine replacement. One such regimen is listed here.[24]

After appropriate laboratory testing has been drawn:

- Levothyroxine 200 to 300 μg IV, followed by daily doses of 1.6 μg/kg
- Tri-iodothyronine 10 to 25 μg IV, followed by 2.5 to 10 μg every 8 hours
- Hydrocortisone 100 mg every 8 hours until exclusion of adrenal insufficiency
- Supportive care including ventilator and circulatory support, passive rewarming or IV dextrose as needed
- Treatment of underlying infection
- Treatment of arrhythmias

Psychogenic Causes

Psychiatric or psychological causes of coma may be considered once all medically treatable conditions have been considered and addressed. Such causes include catatonia, psychogenic nonepileptic seizures, conversion disorder, factitious disorder or malingering. The patient's physical examination is the most telling diagnostic test for these entities and consultation with an experienced neurologist may be helpful.

THE FUTURE OF COMA

The Curing Coma Campaign was launched in 2019 and consists of a multidisciplinary scientific advisory committee dedicated to furthering our understanding and treatment of coma. The campaign is organized into 3 pillars. The first pillar includes classification, or endotyping, of different types of coma based on pathophysiology. The second pillar focuses on continuing investigation of neuroprognostic biomarkers, the refinement of which would inform the treating clinician of the expected clinical recovery for each endotype of coma. Finally, the third pillar centers on the efforts to implement proof-of-concept trials targeted at pharmacologic and electrophysiologic interventions to improve outcomes for patients with disorders of consciousness.[25] This concerted international mission holds the potential to advance our current prognostication practice patterns and to improve the long-term outcomes of comatose patients.

DISCLOSURE

The authors have nothing to disclose.

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