BMJ Best Practice

Evaluation of coma

Straight to the point of care

Last updated: Jul 18, 2024

Table of Contents

Summary

Definitions

Coma is the absence of consciousness.

- This state of unarousable unconsciousness includes the failure of eye opening to stimulation, a motor response no better than simple withdrawal-type movements, and a verbal response no better than simple vocalization of nonword sounds. This presupposes that the motor pathways and systems that would allow a conscious patient to respond are intact.[1] [2] [3]

Full consciousness is an awake state in which one is aware of oneself and the environment, including the ability to perceive and interpret stimuli and to interact and communicate with others in the absence of motor deficits.

- Basic alerting and wakefulness is a function of the ascending reticular activating system (ARAS).
- Awareness is more complex and incompletely understood. It has multiple hierarchies (the highest probably being self-awareness and apperception) and components (e.g., perception, memory, attention, language and other symbolic coding, emotion, motivation, response selection). These components of awareness, and full conscious awareness itself, are now thought to relate to the integrated action of networks of cerebral cortical regions.[4] In the assessment of conscious awareness, the Coma Recovery Scale-Revised (CRS-R) is useful in grading and tracking the level of consciousness.[5]

Brain death

- The irreversible, total destruction of all brainstem functions, including the capacity for alertness, cranial nerve functions, and apnea (UK), or all brain function (whole brain death in US).
- There are guidelines for the neurologic determination of death in infants, children, and adults.[6]
- Brain death must never be diagnosed without an etiology.

Vegetative state (unresponsive wakefulness syndrome [UWS])

- The complete loss of awareness with preserved wakefulness and wake-sleep-cycles. Thalamocortical function is severely disrupted. VS is commonly due to severe cerebral cortical damage (usually by anoxia-ischemia after cardiac arrest or less commonly by hypoglycemia), by damage to the white matter of the cerebrum (most commonly related to diffuse axonal injury from traumatic brain injury), or thalamic damage (by anoxia-ischemia or structural lesions such as tumors or strokes). A new term, UWS, is gradually replacing VS as some patients who are behaviorally unresponsive may have “covert awareness”, as revealed by specialized testing such as functional magnetic resonance imaging (fMRI).[7]

Minimally conscious state (MCS)

- The preservation of 1 or a very few elements of awareness: for example, behaviorally fixating or following with the eyes and reaching purposefully for an object.

Delirium

- More isolated/focal aspect of impaired awareness in which attention or selection and maintenance of mental concentration is the key feature.

- Alerting/wakefulness is preserved to a large degree.

Neglect syndrome

- More isolated/focal aspect of impaired awareness most commonly seen with lesions of the nondominant parietal lobe or prefrontal cortex.
- Alerting/wakefulness is preserved to a large degree.

Encephalopathy

- Diffuse disturbance of cerebral function in the absence of overt parenchymal inflammation or structural abnormality.
- There are numerous encephalopathies due to electrolyte disturbances, disturbances in thyroid function, inborn errors of metabolism (e.g., porphyria, mitochondrial disorders), organ failure (e.g., hepatic encephalopathy), systemic inflammation (e.g., due to burns), and cardiac arrest (anoxic-ischemic encephalopathy). Most of these cause reversible, functional dysfunction of the ARAS and cause a more diffuse disturbance without localizing signs.

Mass lesion

- Includes brain abscess, tumor, intracerebral hemorrhage, and trauma with epidural or subdural hematoma.
- Depending on the case mix, mass lesions causing coma are common, especially in centers with patients with trauma, cancer, or stroke, and even in general hospitals.
- It is important to recognize early phases of herniation syndromes (caused by shifts of brain structures from one compartment to another), and to investigate and treat before irreversible damage occurs. Consciousness is impaired due to compression of ARAS components.
- In subfalcine herniation, the midline structures of the supratentorial space are laterally displaced, causing pressure on the thalamus and progressive impairment of consciousness with or without hemiparesis, and oculomotor palsy in later stages.
- With transtentorial herniation there is downward displacement of the uncus (uncal herniation) or diencephalic structures (thalamus and hypothalamus) through the tentorial opening. This causes brainstem compression with early oculomotor palsy often before loss of consciousness.
- Tonsillar herniation through the foramen magnum compresses the caudal medullary respiratory center, causing respiratory arrest and brain death.
- Central (diencephalic) herniation is said to be common. Compression of the midbrain produces irreversible bilateral oculomotor palsies in later stages.
- Rostrocaudal deterioration of brainstem function occurs with brainstem distortion affecting microvascular perfusion of tissue. Loss of consciousness is typically abrupt with cranial nerve palsies.

Disorders mimicking comas

- Locked-in state is when consciousness is preserved but motor output is impaired (e.g., due to basis pontis lesions, severe polyneuropathies such as Guillain-Barre syndrome or pharmacologic paralysis).
- Psychogenic unresponsiveness relates to lack of responsiveness due to psychogenic causes, in the absence of any toxic, metabolic, inflammatory, or structural damage to the brain (e.g., pseudocoma, pseudoseizure, psychogenic seizures).

Transient coma

- Syncope (fainting) is a transient coma due to the temporary reduction of global brain perfusion, which can be due to cardiac etiologies, vasomotor etiologies, orthostatic hypotension, or pulmonary embolism.
- Seizures produce transient coma due to epileptiform discharges in the brain, either as absence/petit mal seizures (bifrontal or diffuse cortical and thalamic involvement), focal unaware seizures (usually of temporal lobe origin, associated with diffuse limbic involvement and cerebral cortical inhibition), or generalized convulsive seizures (with seizure discharges involving both cerebral hemispheres and brainstem structures). Coma can be prolonged in status epilepticus (e.g., nonconvulsive status epilepticus as diagnosed by EEG). Convulsive movements and incontinence can occur, especially with generalized tonic-clonic seizures.
- Concussion is the transient impairment of consciousness due to a forceful displacement of the brain (e.g., by a blow to the head or sudden acceleration or deceleration).

Pathophysiology

Alerting or arousal is a function of the ARAS. Arousal to wakefulness is a prerequisite for awareness. This arousal system is anatomically represented by several structures in the rostral brainstem tegmentum, the diencephalon, and projections to the cerebral cortex.[8] Principal among these are acetyl choline-producing neurons in the rostral brainstem. These project rostrally in 2 major pathways that also contribute to cortical arousal:[8]

- A dorsal pathway that synapses with the midline and nonspecific thalamic nuclei, which then send a glutaminergic projection to large areas of the cerebral cortex
- A ventral pathway from the rostral brainstem tegmentum that reaches the basal forebrain, especially the posterior hypothalamus, where axon terminals act on neurons that synthesize histamine, hypocretin, or orexin.

The ARAS is a complex system with some redundancy of pathways that are involved in arousal and maintenance of wakefulness. This may explain the recovery of the arousal system after initial coma, almost always within 3 weeks from coma onset in most patients. As a corollary, disorders cause impaired consciousness by impairing the function of a significant component of the ARAS.

Epidemiology

Although transient episodes of unconsciousness (e.g., faint, seizure) are common and account for about 5% of emergency room visits, in-hospital consultations for coma constitute only 0.02% of admissions in England.[9] Adult men and women are almost equally affected. The mean age is 57 years, although >35% of patients with coma are >75 years of age.[9]

Prevention and management

Initial management steps include airway, breathing, and circulatory (ABC) support. In the unresponsive patient, airway protection is paramount.[10]

Clinical assessment tools for patients with impaired consciousness, include the Glasgow Coma Scale and the Full Outline of UnResponsiveness (FOUR) scoring system; the latter has advantages in intubated patients.[11]

Guidelines inform the prevention and management of ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and trauma.[12] [13] [14] [15][16] [17][18][19] [20] [21] The use of pharmacological

and electrical stimulation in cases of vegetative (UWS) and minimally conscious states remains controversial.[22]

Etiology

Etiologies can be broadly grouped into vascular, infective, neurological, metabolic, environmental, toxic, and coma mimics. The relative proportion of etiologies varies across and within countries depending on the nature of the hospital for the case mix of patients. Etiologies also vary in their degree of reversibility. Some (e.g., ischemia, trauma, and hemorrhage) can cause irreversible damage. Most cases of metabolic disorders are reversible, but some (e.g., Wernicke encephalopathy, hypoglycemic encephalopathy) can cause permanent deficits.

Vascular

Vascular causes of coma include stroke (ischemic and hemorrhagic), subarachnoid hemorrhage, cardiac arrest, basilar artery thrombosis, cerebral vein thrombosis, and hypertensive encephalopathy (with or without posterior reversible encephalopathy syndrome [PRES]).

Ischemic stroke

- Features of ischemic stroke depend on the affected vascular territory.
- Can produce coma if components of the ascending reticular activating system (ARAS) are affected.
- Coma occurs with brain swelling/cerebral edema, with herniation phenomena, or with seizures (in about 1% of acute ischemic strokes).
- Left or dominant cerebral infarction can cause transient loss of consciousness in the acute phase. Swelling and herniation (especially with cerebral hemispheric infarction and horizontal displacement of midline structures or brainstem compression with cerebellar infarction), can produce coma of long duration. Severe strokes are often fatal without surgical decompression.

Hemorrhagic stroke

- Intracerebral hemorrhages are common and usually caused by the rupture of small arteries (due to vascular wall damage from severe, sustained hypertension).
- Can produce coma if there is mass effect/herniation syndrome with pressure on the thalamus or with rupture into the ventricular system.
- Coma is due to seizure activity in about 1% of cases.

Subarachnoid hemorrhage (SAH)

- Most are due to ruptured saccular (berry) aneurysms that are at branch points of the circle of Willis arteries.
- Consciousness may be lost temporarily or permanently depending on the extent of the hemorrhage.
- Most medical centers see about 1 case a month on average.[23]
- Prompt recognition and neurosurgical referral are essential.

Cerebral venous thrombosis

- Deep cerebral vein involvement leads to coma if there is thalamic involvement. Alternatively, coma can result from bilateral cerebral venous infarction or hemorrhage, or from mass effect with herniation or seizures (seizures are common in cortical vein thrombosis).
- More than one third of cases are in the setting of a hypercoagulable state (e.g., factor V Leiden; deficiency of protein C, protein S, or antithrombin; polycythemia, thrombocytosis, paroxysmal nocturnal hemoglobinuria, or pregnancy).

- The situation can become extreme with extensive thrombosis of the deep cerebral venous system.

Hypertensive encephalopathy

- With malignant or accelerated hypertension, cerebral edema occurs with focal or widespread/generalized impairment of cerebral function.
- The circulation to the posterior cerebrum seems the most vulnerable, causing PRES.

Cardiac arrest

- Anoxic-ischemic encephalopathy can occur after cardiac arrest.
- Causes a global disturbance in cerebral function.

Infectious

Infective causes of coma include sepsis, meningitis, brain abscess, and encephalitis. Systemic infection is usually reversible.[24]

Sepsis-associated encephalopathy[24]

- The proposed mechanism includes impaired microcirculation, altered brain neurotransmission, cytokines, generation of free radicals, and secondary effects from the failure of other organs.
- Mortality is up to 70% in some patient groups, but patients die from multiorgan failure rather than nervous system complications.[25]

Meningitis

- Coma in bacterial meningitis can result from the toxic effects of inflammatory mediators, followed by secondary complications (e.g., cerebral edema, obstructive and communicating hydrocephalus, seizure activity), and the cerebrovascular complications of arteritis, ischemic and hemorrhagic infarctions, and septic venous sinus thrombosis.
- Fungal meningitis and meningitis due to parasites, such as toxoplasmosis, probably share some of these mechanisms.
- The encephalopathy that accompanies meningitis probably shares some of the mechanisms found in sepsis-associated encephalopathy.

Encephalitis

- Viral encephalitis occurs due to indirect or direct viral infection of the brain from viruses including herpes simplex virus, West Nile virus, and rabies virus.
- Autoimmune encephalitis also occurs.[26] [27] [28] This may be a postinfectious phenomenon: for example, after infectious mononucleosis or measles or rubella. Alternatively, antigen-specific encephalitides are commonly, but not invariably, paraneoplastic syndromes. They often respond to immunosuppressive therapy.
- The incidence is about 2.2 per million population per year.[29]

Brain abscess

- Produces a supratentorial mass lesion and may lead to herniation syndrome.
- Prompt evaluation and urgent CT are indicated.

Neurological

Neurological causes of coma include traumatic brain injury, brain tumor, syncope, and seizure disorder.

Traumatic brain injury

- Coma that occurs immediately following trauma can range from primary injury, including concussion and diffuse axonal injury (DAI), to brain death. Secondary brain injury (e.g., from subdural and epidural hematoma) can cause coma with onset after a lucid interval, or as a complication of concussion or DAI (characteristically without such a lucid period). Occasionally status epilepticus can be responsible.
- Concussion is the transient loss of consciousness after a blow to the head and is often accompanied by amnesia.[30] Several hypotheses have been proposed (e.g., the vascular theory, the convulsive theory, the reticular theory), but none has been established or accepted.[30] [31] [32]
- Talk and die" syndrome is concussion followed by a lucid interval then impaired consciousness. This may be due to acute subdural or epidural hematoma, which should be ruled out with neuroimaging.
- DAI is characterized by loss of consciousness at the time of the trauma and it is produced by forces causing shearing injuries to the cerebral white matter and the brainstem in severe injuries.[33]
- Secondary brain injury refers to insults to the injured brain that evolve after the initial injury.[34] They are often detectable, preventable, and treatable. These include intracranial hemorrhage (bleeding into the brain parenchyma or the extracerebral subarachnoid, subdural, or epidural space) and raised intracranial pressure (ICP) due to increased mass from blood or tissue edema. In general, it is advisable to monitor ICP in any patient with traumatic brain injury and Glasgow Coma Scale score ≤8.
- Patients with acute structural brain lesions, including traumatic brain injury, have a higher incidence of nonconvulsive status epilepticus, approaching 20%.[35] Continuous EEG monitoring for 24 to 48 hours will capture >80% of these seizures, which would go undetected without such monitoring.
- Special consideration should be given to the patient's age at the time of the injury. If aggressive measures for investigation and treatment are indicated, improvement should be realized within 3 days; if not, the patient should be prognostically re-evaluated and goals reassessed.[36]

Brain tumor

- Not a common cause of coma.
- Produces a supratentorial mass lesion and may lead to herniation syndrome.
- Prompt evaluation and urgent CT are indicated.

Seizure disorder

- Seizures cause transient coma due to abnormally rapid discharges of neurons in the brain.
- Classed as partial seizures (cause impaired consciousness if spread diffusely in the limbic system or to the thalamus, producing nonconvulsive seizures or secondary generalized convulsive seizures) or primary generalized seizures (e.g., absence, atypical absence and convulsive, atonic).

Syncope/fainting

- Transient coma subsequent to the brief reduction of global brain perfusion due to cardiac etiologies, vasomotor etiologies, orthostatic hypotension, or pulmonary embolism.[37] Recovery of consciousness and orientation is usually abrupt. Brief convulsive movements and incontinence can occur.

Metabolic

Wernicke encephalopathy

- Alcohol use disorder, with nutritional deficiency, is the most common etiologic factor, but may occur in any susceptible patient (e.g., with intestinal obstruction).
- History is compatible with vitamin B deficiency.
- Promptly giving parenteral thiamine (50-100 mg) is required.

Electrolyte or endocrine disorder

- Namely, glucose, sodium, calcium, phosphate, and magnesium abnormalities.
- Diabetic ketoacidosis (DKA) is a common cause of coma but severe nonketotic hyperglycemia (NKH) is not common.
- Hypothyroidism is common (2% of adult women) but myxedema coma (life-threatening complication) is relatively rare.[38]
- Thyroid storm is a rare cause of coma, induced by excessive release of thyroid hormones in patients with hyperthyroidism.
- Mostly cause reversible, functional dysfunction of the ARAS and a more diffuse disturbance without localizing signs.
- It seems likely that these disorders impair the polysynaptic function of the ARAS.

Inborn errors of metabolism

- For example, porphyria, mitochondrial disorder.
- Most cause reversible, functional dysfunction of the ARAS and cause a more diffuse disturbance without localizing signs.
- It seems likely that these disorders impair the polysynaptic function of the ARAS.

Environmental

Hypothermia

- Hypothermia is defined as a core body temperature <95°F (35°C), but as a primary cause of coma the temperature is usually <82.4°F (28°C).
- May be accidental, primary (usually due to a hypothalamic disorder), or secondary to loss of autonomic function, as in high spinal cord injuries, hypothyroidism, adrenal failure, Wernicke encephalopathy, advanced sepsis, or sedative drug intoxication. In hypothyroidism, adrenal failure, Wernicke encephalopathy, advanced sepsis, and sedative drug intoxication, the coma is usually due to the underlying condition rather than the hypothermia itself.

Hyperthermia

- Hyperthermia or fever is defined as a body temperature of >101.3°F (38.5°C). Temperatures of >107.6°F (42°C) directly produce encephalopathy, slowing of EEG rhythms, and often seizures.
- Hyperthermia may occur due to disorders of heat production (due to malignant hyperthermia, thyrotoxicosis, neuroleptic malignant syndrome, cocaine or amphetamine abuse, salicylate intoxication, or convulsive status epilepticus), diminished heat dissipation (due to heat stroke, autonomic dysfunction, use of anticholinergic medications, and a hot environment), or hypothalamic dysfunction (due to strokes, trauma, or encephalitis affecting temperature-regulating centers).

Burns

- Systemic inflammation due to burns can cause an encephalopathy that is usually reversible and resembles metabolic encephalopathies.[24]

- Proposed mechanisms include impaired microcirculation (similar to that found in other organs in sepsis), plasma amino acid imbalance, cytokine effect, free radicals effect, and secondary effects from the failure of other organs.[24]

Toxic

Carbon monoxide poisoning

- Accounts for >40,000 emergency room visits in the US annually.[39]
- Common in winter months or in patients found comatose following exposure to internal combustion engine exhaust (vehicle or generator).
- Pulse oximeters overestimate oxygen concentration, but it is important to treat these patients promptly with 100% oxygen or hyperbaric oxygen to help displace the carbon monoxide from the hemoglobin.

Substance abuse and overdose

- Alcohol, methanol, and ethylene glycol (antifreeze) ingestion may all induce coma.
- Knowledge of the principal toxidromes can be of considerable help to the clinician in raising suspicions of specific drug intoxications. These include lysergic acid diethylamide (LSD), cocaine, amphetamines, opioids, sedatives, ethanol, organophosphates, carbamate insecticides, jimson weed, deadly nightshade, ephedrine, pseudoephedrine, alpha-2 agonists, sedatives, first-generation antihistamines, tricyclic antidepressants, and benztropine.

Syndrome	Drug Examples	Features
Sympathomimetic	Cocaine, amphetamines, lysergic acid diethylamide, ephedrine, pseudoephedrine	Increased heart rate and blood pressure; pupils are dilated but reactive, sweating, agitation, hallucinations, seizures
Sympatholytic	Opiates, alpha-2 agonists, sedatives, ethanol	Small but reactive pupils, hypotension, bradycardia, respiratory depression
Cholinergic syndrome	Organophosphates, carbamate insecticides	Increased sweating, small pupils, increased sweating, salivation, bronchial secretions and gastrointestinal activity, confusion, seizures, coma, respiratory failure
Anticholinergic syndrome	First-generation antihistamines, tricyclic antidepressants, benztropine, jimson weed, deadly nightshade	Pupils dilated and often unreactive, tachycardia, decreased sweating, ileus, fever, urinary retention

The principal toxidromes, a constellation of features peculiar to certain classes of drugs

Table created by G. Bryan Young, MD; used with permission

Disorders mimicking coma

Psychogenic unresponsiveness and locked-in states may both be confused with coma. More importantly, locked-in state may even be confused with brain death.[40]

Psychogenic unresponsiveness may manifest as pseudocoma or nonepileptic seizures (pseudoseizures/psychogenic seizures). Although pseudocoma is uncommon, nonepileptic (pseudo) seizures make up about one third of admissions to epilepsy units.[41] There is often a background of psychosocial problems and abuse, as well as a lack of response to antiepileptic medications. Onset of psychogenic unresponsiveness in childhood or age >60 years is uncommon, but can occur. Most patients are women.[1]

Locked-in state is uncommon. Patients with locked-in state have preserved consciousness but impaired motor output. This includes patients with basis pontis lesions, severe polyneuropathies (e.g., Guillain-Barre syndrome, acute inflammatory demyelinating polyneuropathy), pharmacologic neuromuscular paralysis, and central pontine myelinolysis. Basis pontis lesions might be caused by an occlusion of the basilar artery, hypertensive hemorrhage, or central pontine myelinolysis. Central pontine myelinolysis typically occurs in systemically ill inpatients with sudden electrolyte disturbance. Pharmacologic paralysis most often occurs in the ICU or postsurgical recovery room, as a result of slow clearance or metabolism of neuromuscular blocking agents.

Urgent considerations

(See **Differentials** for more details)
Acutely impaired or deteriorating level of consciousness constitutes an emergency. Such patients need to be assessed urgently from both neurological and general (especially cardiovascular-pulmonary) perspectives. It is usually necessary to have a team of doctors and nurses tackle these problems simultaneously. Airway protection and attention to vital sign abnormalities take priority.

Airways management

In the unconscious patient, the airway may be blocked due to obstruction of the pharynx by the tongue, vomit, or a foreign body. The airway should be cleared by suction and by “head tilt and chin lift” technique or the modified “chin thrust” if there is concern about cervical spine stability. Lying the patient on his or her side is often sufficient for the patient obtunded after a convulsive seizure, as respirations should be adequate and consciousness often recovers quickly without the need for an oral airway (may induce vomiting) or endotracheal intubation. If it is anticipated that the patient may remain comatose for a longer time, or if there already has been aspiration of secretions, an endotracheal tube is placed. Adequate oxygenation often requires the supplemental administration of higher percentages of oxygen (e.g., 60% to 100%).

Shock

The patient with shock will look unwell and often have symptoms specific to the underlying cause (e.g., fever, chest pain, shortness of breath, or abdominal pain). This may be difficult to recognize in practice.

Shock, with impaired tissue perfusion, sometimes precedes a drop in blood pressure. The following signs raise the suspicion of shock and impending blood pressure fall: tachycardia, cool extremities, weak peripheral pulses, prolonged capillary refill (>2 seconds), and narrowing of the pulse pressure (<25 mmHg). Restoring blood volume and providing inotropic support are often necessary. Vasopressors can help raise the blood pressure, but might impair peripheral perfusion.

Overdose

Signs of opioid overdose include small, reactive pupils, hypoventilation, bradycardia, and hypothermia. Such patients need prompt airway, respiratory, and circulatory support, including endotracheal intubation, intravenous volume replacement, and the administration of an opioid antagonist. Naloxone is usually given intravenously in repeated doses. The effect is usually prompt recovery, but it may be short-lasting.

Overdose with tricyclic antidepressants (TCA), such as amitriptyline, in addition to causing impaired consciousness (from blocking the reuptake of various aminergic neurotransmitters), produces prominent anticholinergic effects. Such patients may develop seizures, bradycardia, hypotension, and various ventricular arrhythmias. The ECG can provide clues for TCA toxicity: the last 40 msec of the QRS complex shows a right axis deviation; R wave >S wave amplitude or >3 mm in aVR; and prolongation of the QRS complex. In addition to activated charcoal through the nasogastric tube, respiratory, airway, and circulatory support, and repeated doses of physostigmine, can help reverse the anticholinergic toxicity. Cardiac pacing is sometimes necessary. Seizures may require antiepileptic drug therapy.

Wernicke encephalopathy

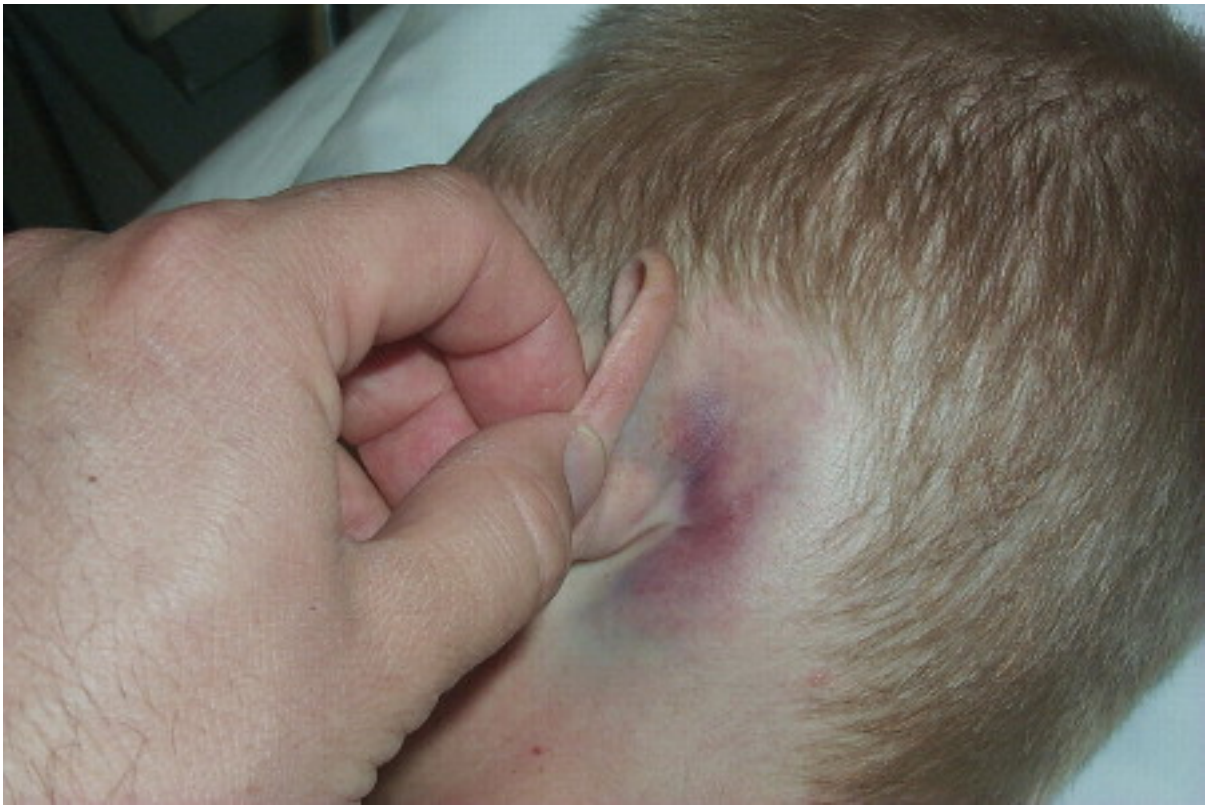
There are usually preserved pupillary reflexes with ocular movement palsies of absent vestibular-ocular reflexes.[42] [43] This is a classic presentation but can be mimicked by drug overdose. The triad of ataxia,

ophthalmoplegia, and encephalopathy is not always present. Wernicke encephalopathy may also feature with hypothermia and coma, and in patients with histories compatible with vitamin B deficiency (alcoholic people, nutritionally deprived patients, those with gastric stapling, or patients on hemodialysis not taking supplemental B vitamins). Blood tests for pyruvate and erythrocyte transketolase are important, and parenteral thiamine (50-100 mg) is required promptly. Carbohydrate loading should be avoided until this is done. MRI shows increased signal on fluid-attenuated inversion recovery (FLAIR) in mammillary bodies, hypothalamus, medial thalamus, and floor of fourth ventricle. Treatment includes stabilization and resuscitation with airway protection if necessary, high-dose parenteral thiamine, correction of magnesium deficiency, and multivitamin supplementation.

Head injury

Evidence of trauma is often available historically, but not always. Bruising should be looked for, especially linear bruising. Signs of significant head trauma, with basal skull fractures, include hemotympanum, Battle sign (bruising over the mastoids), and raccoon eyes (indicating a fracture of the orbital roof).

In the “talk and die” syndrome, the patient has concussion, recovers consciousness (lucid interval), and then deteriorates to stupor and then coma, usually due to acute subdural or epidural hematoma. It is important to look for lateralized findings, such as gaze preference or conjugate eye deviation to one side, asymmetry of limb movements or frank hemiplegia, and/or pupillary asymmetry (usually there is dilation of the pupil ipsilateral to the lesion; note that about 20% of people have anisocoria). This is followed by loss of ipsilateral pupillary reactivity and paralysis of adduction of the eye. In the later stages the opposite pupil loses its reactivity, due to intrinsic midbrain damage from herniation.[44] Prompt evaluation and action including supportive airway and blood pressure care is required. Urgent CT is indicated. Recognizing early phases of herniation syndromes is important, and investigations and treatments should begin before irreversible damage occurs. Treatment with intravenous mannitol or hypertonic saline and other measures (elevation of the head by 30° in a midline position; supportive ventilation) can provide time before neurosurgical intervention and can be life-saving. Current guideline recommendations on the management of people with traumatic brain injury should be followed.[17][18] See Mild traumatic brain injury and Skull fractures .



Battle's sign: superficial ecchymosis over the mastoid process

van Dijk GW. Practical Neurology. 2011;11(1):50-55; used with permission

Basilar artery thrombosis

Symptoms are of occipital lobe ischemia (photopsia, visual loss) and signs include quadriparesis, pseudobulbar palsy, pupillary palsies, and ocular palsies.[45] MRI or CT angiogram shows basilar artery occlusion, either in the proximal portion (top of the basilar syndrome, usually with midbrain and thalamic damage) or more extensively. Treatment in early presentations is thrombolysis with intravenous or intra-arterial recombinant thromboplastin activator (rTPA). This can reverse the ischemic damage, which is often fatal if untreated.

Hypoglycemia

Cold perspiration, confusion, or lightheadedness/agitation precedes loss of consciousness. Seizures, multifocal or generalized, should also prompt consideration or screening for hypoglycemia.[46] Point-of-care testing usually allows for recognition of hypoglycemia.

Prompt administration of dextrose is required. In the comatose patient, give intravenous dextrose immediately if the patient has intravenous access.[47] [48] [49] If intravenous access is not available (e.g., in an outpatient setting), give glucagon or dasiglucagon, although dextrose is preferred if available.[47][49] [50]

If the patient has recurrent episodes of hypoglycemia, give a dextrose intravenous infusion in order to sustain euglycemia.[51]

In the patient who may be nutritionally deprived it is wise to pre-administer thiamine to prevent Wernicke encephalopathy.

Myxedema coma

Patients often appear pale and edematous, and there is often puffiness around the eyes. Systemically, they may be hypothermic and have respiratory failure with hypercarpnia. There is often a past history of hypothyroidism, treated hyperthyroidism, head injury, or pituitary surgery (central cause). Serum thyroxine (T4) and triiodothyronine (T3) are depressed. Serum thyroid-stimulating hormone (TSH) is elevated in thyroid gland failure, while TSH is abnormally low in central hypothyroidism. Replacement of T4 or T3 should be incremented gradually in patients with cardiovascular disease. In cases of central hypothyroidism, or if hypothyroidism is longstanding, pretreatment with corticosteroids such as hydrocortisone is recommended to avoid "adrenal crisis."

Cerebral venous thrombosis

It is important to consider this as a diagnosis when patients present with headache of subacute onset that is intractable and worsening, and often associated with nausea and vomiting.[52] Seizures are also common if the cortical vein is involved. Deep cerebral vein involvement leads to coma with thalamic involvement. Urgent MRI (with venous phase) or CT angiogram (with venous follow-through) is required. Prompt recognition and heparinization or thrombolysis is often life-saving. Anticoagulation is required and used even in the presence of intraparenchymal hemorrhage.[53] Continued thrombosis, cerebral edema, and hemorrhage will continue if untreated. Thrombolysis is considered in extreme situations (e.g., extensive thrombosis of deep cerebral venous system). Anticonvulsants are used for seizures.

Bacterial meningitis

This should be considered in the presence of any 2 of: fever, headache, nuchal rigidity, or any alteration in mental status before coma.[54] Children also often have vomiting, photophobia, and lethargy. A petechial rash raises the possibility of meningococcal meningitis. Blood cultures and empirical antibiotics should be initiated while requesting CT or MRI scan. If neuroimaging is negative for mass effect, lumbar puncture is required. Empirical therapy is often indicated initially, until the specific organism and its sensitivities are known. If indicated, empirical therapy should be started immediately according to local sensitivities and protocols. See Bacterial meningitis in adults and Meningococcal disease .

Purulent meningitis is usually fatal if not treated and carries a high morbidity if treatment is delayed. For penicillin-sensitive *Streptococcus pneumoniae* , penicillin G, cefepime, ceftriaxone, or cefotaxime is suitable. For penicillin-resistant forms the latter 3 are used. For *Neisseria meningitidis* , penicillin G or ampicillin is suitable. For *Haemophilus influenzae* , ceftriaxone, cefotaxime, or cefepime is suggested. These should be given intravenously at appropriate doses for 10 to 14 days.

Encephalitis

An acute or subacute onset of a febrile illness, altered mental status, focal neurological abnormalities, and seizures raises suspicion for this condition. This is a medical emergency; hence, management consists of basic resuscitation measures ensuring adequacy of the airway, breathing, and circulation, and empirical antiviral therapy in cases of suspected viral encephalitis concurrently with diagnostic steps. All suspected cases of encephalitis should be admitted and fully evaluated. Some patients with milder symptoms and signs can be managed in a regular nursing unit, with access to an intensive care unit (ICU) bed if needed. All other patients, and in particular those with complications (e.g., significant electrolyte abnormalities, strokes, elevated intracranial pressure, cerebral edema, coma, seizure activity, or status epilepticus) should be managed in an ICU, preferably a neuro-intensive care unit.

Prompt isolation is required for all forms of encephalitis until the etiology is determined; encephalitides with airborne or contact transmission to immunocompetent hosts (herpes simplex virus [HSV], varicella, mumps, rubella, enteroviruses, upper respiratory viral infections) require mandatory isolation. Less common infectious causes should involve close collaboration between the clinicians and microbiologists/virologists.

Etiology is often obscure, and therefore no specific measures exist for the majority of the cases. However, for cases where a diagnosis is reasonably certain, treatment is directed toward the underlying offending agent (e.g., antivirals for viral encephalitis). Even when the diagnosis is certain, treatments are not available for many of the encephalitides. All cases of suspected community-acquired viral encephalitis are started empirically on acyclovir until the infecting virus is determined. In an immunocompromised patient, cytomegalovirus encephalitis is a consideration. If suspected, ganciclovir and foscarnet are given with acyclovir until a viral cause is either confirmed or excluded.

Sepsis

Sepsis is a spectrum of disease, where there is a systemic and dysregulated host response to an infection.[55]

Presentation ranges from subtle, nonspecific symptoms (e.g., feeling unwell with a normal temperature) to severe symptoms with evidence of multiorgan dysfunction and septic shock. Patients may have signs of tachycardia, tachypnea, hypotension, fever or hypothermia, poor capillary refill, mottled or ashen skin, cyanosis, newly altered mental state, or reduced urine output.[56]

Risk factors for sepsis include: age under 1 year, age over 75 years, frailty, impaired immunity (due to illness or drugs), recent surgery or other invasive procedures, any breach of skin integrity (e.g., cuts, burns), intravenous drug misuse, indwelling lines or catheters, and pregnancy or recent pregnancy.[56]

Early recognition of sepsis is essential because early treatment improves outcomes.[56] [57][Evidence C] [Evidence C] However, detection can be challenging because the clinical presentation of sepsis can be subtle and nonspecific. A low threshold for suspecting sepsis is therefore important. The key to early recognition is the systematic identification of any patient who has signs or symptoms suggestive of infection and is at risk of deterioration due to organ dysfunction.

Screening tools

Several risk stratification approaches have been proposed. All rely on a structured clinical assessment and recording of the patient's vital signs.[56] [58] [59][60][61] It is important to check local guidance for information on which approach your institution recommends. The timeline of ensuing investigations and treatment should be guided by this early assessment.[60]

Sepsis screening tools are designed to promote early identification of sepsis and consist of manual methods or automated use of the electronic health record (EHR). These include the Sequential (or Sepsis-related) Organ Failure Assessment (SOFA) score, the quick SOFA (qSOFA) criteria, National Early Warning Score (NEWS), and Modified Early Warning Score (MEWS). There is wide variation in diagnostic accuracy of these tools but they are an important component of identifying sepsis early for timely intervention.[57]

The Third International Consensus Group (Sepsis-3) recommends using the SOFA score (primarily validated in patients in intensive care), with a score ≥2 in a patient with a suspected infection being suggestive of sepsis.[55]

Although the presence of a positive qSOFA should alert the clinician to the possibility of sepsis in all resource settings, its poor sensitivity has led the Surviving Sepsis Campaign to advise against using the qSOFA compared with National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) as a single screening tool for sepsis or septic shock.[57]

The National Institute for Health and Care Excellence (NICE) UK guideline on sepsis emphasises the need to 'think sepsis' in any patient presenting with possible infection. It recommends structured observations and stratification of risk of severe illness and death according to patient age and setting.[56]

Management of patients with suspected sepsis

Treatment guidelines have been produced by the Surviving Sepsis Campaign and remain the most widely accepted standards.[57] [62]

Recommended treatment of patients with suspected sepsis is:

- Measure lactate level, and remeasure lactate if initial lactate is elevated (>18 mg/dL [>2 mmol/L]).
- Obtain blood cultures before administering antibiotics.
- Administer broad-spectrum antibiotics (with methicillin-resistant *Staphylococcus aureus* [MRSA] coverage if there is high risk of MRSA) for adults with possible septic shock or a high likelihood for sepsis.
- For adults with sepsis or septic shock at high risk of fungal infection, empiric antifungal therapy should be administered.
- Begin rapid administration of crystalloid fluids for hypotension or lactate level ≥36 mg/dL (≥4 mmol/L). Consult local protocols.
- Administer vasopressors peripherally if hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg, rather than delaying initiation until central venous access is secured. Norepinephrine (noradrenaline) is the vasopressor of choice.
- For adults with sepsis-induced hypoxemic respiratory failure, high flow nasal oxygen should be given.

Ideally these interventions should all begin in the first hour after sepsis recognition.[62]

For adults with possible sepsis without shock, if concern for infection persists, antibiotics should be given within 3 hours from the time when sepsis was first recognized.[57] For adults with a low likelihood of infection and without shock, antibiotics can be deferred while continuing to closely monitor the patient.[57]

See Sepsis in adults and Sepsis in children .

Hypophosphatemia

Hypophosphatemia (refeeding syndrome) most commonly occurs in malnourished patients who are fed in the hospital, causing a shift of phosphate ions from the blood to the intracellular compartment.[63] Marked lowering of serum phosphate, usually to <1.5 mg/dL or 0.5 mmol/L, can produce an acute encephalopathy with seizures, myoclonus, and coma. Severe weakness due to a profound myopathy may necessitate assisted ventilation. It is important to measure serum phosphate in malnourished patients who develop the above features and, if phosphate is low, to replace it intravenously.

Posterior reversible encephalopathy syndrome (PRES)

PRES may be caused by hypertensive encephalopathy, acute hypertension of pregnancy, sepsis, and certain drugs (e.g., cyclosporine and tacrolimus).[64] It occurs with acute/subacute elevations of blood pressure to

levels that overcome cerebral autoregulation (e.g., 240/130 mmHg). This may produce vasogenic edema, usually most marked in the white matter of the posterior parts of the cerebral hemispheres, and associated with cortical blindness and convulsive seizures. Loss of vision (cortical blindness) and seizures may precede loss of consciousness. MRI scans are helpful and show edema of the white matter of the occipital lobes, variably extending anteriorly. It is important to lower the blood pressure and to treat seizures symptomatically, as the condition can totally resolve. Fatal intracerebral hemorrhage has occurred in some patients with associated hematological disorders: for example, disseminated intravascular coagulation. Patients with pregnancy-induced hypertension with eclampsia are optimally treated with magnesium sulfate.

Subarachnoid hemorrhage (SAH)

SAH presents with an initial severe headache that is described as the "worst ever" headache and peaks immediately.[65] In 30% of patients this is coincident with abrupt loss of consciousness due to a rapid rise in intracranial pressure. Signs of meningeal irritation (neck stiffness to forward flexion) may be present, but are often absent if the patient is comatose. Finding a retinal or preretinal (subhyaloid) hemorrhage on funduscopy is diagnostic. Early third nerve palsy is often due to damage to the oculomotor nerve by a posterior communicating artery aneurysm or from early herniation by a temporal lobe hematoma (e.g., with middle cerebral artery aneurysm rupture).

Most medical centers see about 1 case a month on average.[23] Prompt recognition and neurosurgical referral are essential. Aneurysmal clipping or coiling is effective in preventing rebleeding, which carries a high mortality. Neurosurgeons may need to insert an intraventricular drain before coiling or clipping the aneurysm. Vasospasm can cause secondary ischemic stroke after 4 days from the ictus. It is necessary to monitor for this clinically and with transcranial Doppler or repeated angiograms. The effects of vasospasm can be ameliorated by special therapies (induced hypertension, hypervolemia, and hypoviscosity, vasodilating drugs, or angioplasty). Nimodipine and statins are commonly used prophylactically.

Hypothermia

Hypothermia is defined as a core body temperature <95°F (35°C), but as a primary cause of coma the temperature is usually <82.4°F (28°C).[66] Coma is preceded by delirium and then stupor, almost in a dose-dependent manner. At temperatures <82.4°F (28°C), the pupillary light reflex is lost and the patient may appear to be brain dead. There is also a risk of ventricular fibrillation and cardiac arrest. EEG shows evolutionary changes with slowing at 86°F (30°C) and changes to a burst-suppression pattern between 68°F and 71.6°F (20°C to 22°C), and becomes isoelectric at 68°F (20°C). This presumably reflects a progressive failure of synaptic transmission in the brain. There is also a progressive decrease in cerebral blood flow (CBF) by 6% for each 1.8°F (1°C) drop in body temperature. At <77°F (25°C), CBF becomes pressure-passive with loss of autoregulation. Hypothermia may be accidental, primary (usually due to a hypothalamic disorder), or secondary to loss of autonomic function (as in high spinal cord injuries, hypothyroidism, adrenal failure, Wernicke encephalopathy, advanced sepsis, or sedative drug intoxication). In hypothyroidism, adrenal failure, Wernicke encephalopathy, advanced sepsis, or sedative drug intoxication, the coma is usually due to the underlying condition rather than the hypothermia itself. Treatment includes gradual rewarming with blankets, external heat, and warm saline. Careful attention to cardiovascular status is essential.

Cardiac arrest

Anoxic-ischemic encephalopathy can occur after cardiac arrest, causing a global disturbance in cerebral function. Features indicating a poor prognosis include loss of pupillary or corneal reflexes by day 3, a motor

response no better than extensor posturing by day 6 or later, bilaterally absent somatosensory evoked responses to peripheral nerve stimulation, and elevation of serum neuronal specific enolase concentrations of >33 micrograms/L.

Prompt lowering of body temperature to 89.6°F to 93.2°F (32°C to 34°C) (hypothermic therapy) may ameliorate neurologic damage.[67] The 2017 AAN guideline for reducing brain injury after cardiac arrest recommends that patients who are comatose after resuscitation from out-of-hospital cardiac arrest, where the initial rhythm was pulseless ventricular tachycardia or ventricular fibrillation, are offered systemic hypothermia targeted at 89.6°F to 93.2°F (32°C to 34°C), based on strong evidence.[68] The evidence supporting the same temperature management for people with an initial rhythm of pulseless electrical activity/asystole was not as strong but the guideline recommends it may be offered. Using a target of 96.8°F(36°C) in all patients was considered to have moderate evidence of effectiveness and the guideline recommends this as an alternative option.[68]

Treatment with CPR, defibrillation, epinephrine, vasopressin, atropine, antiarrhythmics, and/or magnesium may be required. One systematic review and meta-analysis reported good prognostic accuracy for two postarrest (out-of-hospital cardiac arrest, OHCA, and cardiac arrest hospital prognosis, CAHP) prediction models for neurologic outcome after cardiac arrest.[69] Further studies are needed to refine prognostic determination in children who have been resuscitated from cardiac arrest.[70] Special caution must be taken to assure that patients are free of sedative drugs for at least 12 hours before assessment.[71]

Intrinsic brainstem hemorrhage

A commonly fatal hemorrhagic stroke. Often begins in the pons, with pinpoint pupils due to sympathetic pathway damage. If these extend into the midbrain, the pupils become midposition and unreactive. Treatment is seldom feasible, because brainstem damage is extensive and irreversible by the time the patient is comatose.

Approach

It is clinically useful to first consider broad categories of illnesses, after clues are obtained from the history and general and neurological exams. It is helpful to think anatomically and physiologically and to develop a focused approach that will narrow the diagnostic possibilities to a few that can be sorted out with appropriate investigations.[72] [73][74]

History

Just as with awake and communicative patients, the history is vital. This must be obtained from relatives, friends, and eyewitnesses, by phone if necessary. How the patient fell sick or collapsed can give important clues:

- Did the patient have a seizure?
- Was trauma involved?
- Did the patient lose consciousness gradually or was there fluctuation, as might be seen in metabolic disorders or subdural hematoma?
- Was the patient febrile or having chills (suggesting a central nervous system or systemic infection)?

The background of the patient can be important. Did the patient have cancer, profound depression (raising the possibility of drug overdose), or a history of drug or alcohol abuse? Is there an underlying illness, such as diabetes mellitus, adrenal, hepatic, or renal failure, or immunosuppression (either drug-induced or acquired)? What drugs was the patient taking? Hospital records can be helpful, as can medical alert bracelets or other medical information on his/her person.

Symptoms of herniation syndromes

It is important to recognize the features of herniation syndrome in patients with mass lesions (e.g., brain abscess, tumor, intracerebral hemorrhage, trauma with intracerebral or extracerebral hematoma).

- Subfalcine herniation may produce drowsiness with progressive loss of consciousness, one-sided weakness, and/or late visual disturbances.
- Uncal herniation may produce early visual disturbances before loss of consciousness.
- Central (diencephalic) herniation may produce drowsiness with progressive impairment of consciousness and late visual disturbances.
- Rostrocaudal herniation may produce abrupt loss of consciousness with visual disturbances, hearing disturbances, taste disturbances, difficulty swallowing, and/or differences in facial expression/movement.
- Tonsillar herniation may produce difficulty breathing followed by coma.

Period of delirium

- May be present in patients with various metabolic or toxic encephalopathies, including encephalopathy associated with sepsis or the systemic inflammatory response syndrome and with disorders of body temperature (hypothermia and hyperthermia).
- Characterized by the inability to sustain, focus, or shift attention as its principal or essential feature. Other common phenomena include disorientation, poor short-term memory, disturbed wake-sleep cycle, agitation, confusion, and hallucinations or delusions. It is important to recognize, investigate,

and treat cases of delirium promptly, before further deterioration (associated with increased mortality) occurs.

Amnesia

- This is the inability to lay down new memories for a variable period (minutes to days) after the injury.
- Concussion is often accompanied by an anterograde posttraumatic amnesia.
- Amnesia following impairment of consciousness can also be found in some cases of transient metabolic disturbance, such as hypoglycemia, or intoxication with alcohol or sedative drugs.
- Seizures, especially generalized convulsive or focal unaware seizures of temporal lobe origin, can also disrupt memory mechanisms for minutes to hours or more.
- Over two-thirds of patients with aneurysmal subarachnoid hemorrhage (SAH) experience anterograde amnesia, and 17% have retrograde amnesia for time before the ictus.[75]
- Psychogenic "fugue states/twilight states" are typically associated with amnesia.
- Amnesia can follow vertebrobasilar ischemic attacks if the thalamus suffers a more protracted ischemic time. However, this is rare.
- If the medial-inferior aspects of the both temporal lobes are infarcted following ischemic stroke, the patient will have severe memory impairment.

Duration of unconsciousness

- Syncope, seizure, and concussion usually induce transient coma.
- Diffuse axonal injury (DAI) causes loss of consciousness at the time of the trauma, but the duration of coma is much longer than with concussion. Patients usually regain eye opening within 2 to 3 weeks, which is related to the recovery of function of the subcortical arousal systems. The recovery of awareness is variable, ranging from mild impairment to the persistent/permanent vegetative state (unresponsive wakefulness syndrome [UWS]).

Prodromal symptoms

- May be present with syncope and seizure. These are often nonspecific (e.g., nervousness or irritability, the desire to be alone).

Presence of convulsions

- Convulsions may be present with numerous conditions including:
    - syncope (minor)
    - seizures/epilepsy
    - hypoglycemia, hyperglycemia (especially the nonketotic variety)
    - encephalitis
    - cerebral vein thrombosis (if there is cortical vein involvement), other structural brain lesions affecting the cerebral cortex or underlying white matter
    - hyponatremia, hypocalcemia, hypomagnesemia
    - profound hepatic failure
    - uremia
    - hypertensive encephalopathy (including posterior reversible encephalopathy syndrome [PRES])
    - the use of convulsant drugs or agents (cocaine, amphetamines, aminophylline, lidocaine, isoniazid),
    - advanced neurodegenerative conditions

- psychogenic unresponsiveness (pseudoseizures/psychogenic seizures).

Incontinence

- May occur with either syncope or seizures.

Vision disturbances

- Patients with basilar artery thrombosis may present with symptoms of occipital lobe ischemia (photopsia, vision loss).
- Patients with hypertensive encephalopathy may have cortical blindness and convulsive seizures if PRES develops.
- Seizures may cause vision loss due to interference with incoming visual information.

Hallucinations

- Elementary visual hallucinations (e.g., flashing lights in the opposite visual field) may be induced by seizures involving the occipital region.
- Seizures in visual association areas often produce more complex distortions of images: for example, shapes, micropsia, or macropsia (distortions of size).
- More complex visual hallucinations may occur in patients with withdrawal states of psychoses. These patients do not usually have insight into their hallucinations.
- May be present in patients with recreational drug use.

Headache

- Headache and nuchal rigidity may be described by noncomatose patients with meningitis or SAH.
- Cerebral venous thrombosis may be considered with headache of subacute onset that is intractable and worsening and often associated with nausea and vomiting.
- Headaches are less helpful in other conditions, such as trauma, hypoglycemia, systemic inflammatory diseases, large vessel ischemic strokes, seizures, and withdrawal states.

Overseas travel

- Patients with encephalitis may have a history of overseas travel.

Malnutrition

- Patients with Wernicke encephalopathy have a history compatible with vitamin B deficiency (usually people with alcohol dependence, nutritionally deprived patients, those with gastric stapling, or patients on hemodialysis not taking supplemental B vitamins).
- Refeeding syndrome due to hypophosphatemia occurs in patients with previous malnutrition who have had in-hospital feeding.

Carbon monoxide poisoning

- Common in winter months with increased use of heaters.
- Also common in patients attempting suicide by shutting themselves in a garage with a car engine running.

Significant past medical history

- May provide clues to the diagnosis of organ failure encephalopathies, electrolyte disorder encephalopathies, brain tumor, postinfectious encephalitis, and other causes of coma.

Drug history

- May reveal ingestion/overdose of the following agents that may induce coma: ephedrine, pseudoephedrine, opioids, alpha-2 agonists, sedatives, first-generation antihistamines, tricyclic antidepressants, benztropine.

Syndrome	Drug Examples	Features
Sympathomimetic	Cocaine, amphetamines, lysergic acid diethylamide, ephedrine, pseudoephedrine	Increased heart rate and blood pressure; pupils are dilated but reactive, sweating, agitation, hallucinations, seizures
Sympatholytic	Opiates, alpha-2 agonists, sedatives, ethanol	Small but reactive pupils, hypotension, bradycardia, respiratory depression
Cholinergic syndrome	Organophosphates, carbamate insecticides	Increased sweating, small pupils, increased sweating, salivation, bronchial secretions and gastrointestinal activity, confusion, seizures, coma, respiratory failure
Anticholinergic syndrome	First-generation antihistamines, tricyclic antidepressants, benztropine, jimson weed, deadly nightshade	Pupils dilated and often unreactive, tachycardia, decreased sweating, ileus, fever, urinary retention

The principal toxidromes, a constellation of features peculiar to certain classes of drugs

Table created by G. Bryan Young, MD; used with permission

History of substance abuse, poisoning

- May reveal abuse/overdose of the following substances that may induce coma: lysergic acid diethylamide (LSD), cocaine, amphetamines, opioids, sedatives, organophosphates, carbamate insecticides, jimson weed, deadly nightshade, alcohol, methanol, ethylene glycol (antifreeze).
- May indicate the presence of psychogenic unresponsiveness.

Focused general examination

The general exam can give important clues.

Blood pressure

- Marked hypertension may indicate hypertensive encephalopathy or posterior reversible encephalopathy syndrome (PRES). Blood pressure in hypertensive encephalopathy is acutely/subacutely elevated to levels that overcome cerebral autoregulation (e.g., 240/130 mmHg).
- Hypotension may indicate hypovolemic shock.

Pulse oximetry

- In carbon monoxide poisoning, pulse oximetry may overestimate oxygen concentrations.

Core temperature

- Coma is usually induced at core temperatures <82.4°F (28°C) and those >107.6°F (42°C).
- Core temperature <82.4°F (28°C) may be present in patients with environmental hypothermia, hypothyroidism, Wernicke encephalopathy, advanced sepsis, or sedative drug intoxication.
- Core temperature >104°F (40°C) may be present in patients with environmental hyperthermia, cocaine or amphetamine abuse, convulsive status epilepticus, use of anticholinergic medications, stroke, trauma, thyroid storm, or encephalitis.

Skin

- Jaundice, distended veins around the umbilicus, or spider nevi suggest chronic liver failure.
- Pallor, cyanosis.
- Cherry red discoloration of the lips suggests carbon monoxide poisoning, but this is a rare sign and should not be relied on.
- Petechial bleeding raises the possibility of a seizure, thrombotic thrombocytopenic purpura, meningococcal septicemia, Rocky Mountain spotted fever, vasculitis, or septic emboli.
- Needle marks suggest drug abuse.

Head/face

- May be signs of a basal skull fracture with hemotympanum, Battle sign (bruising over the mastoids), and raccoon eyes (indicating a fracture of the orbital roof).
- A bitten tongue is presumptive evidence of a convulsive seizure.
- A preretinal hemorrhage should raise suspicion of a ruptured intracranial aneurysm.
- Roth spots in the retina may signify endocarditis, leukemia, or septic emboli.
- Buccal pigmentation could indicate underlying adrenal insufficiency.
- The presence of a goiter or Graves ophthalmopathy should prompt suspicion of thyroid storm.

Coma scoring scales

The Glasgow Coma Scale and Full Outline of UnResponsiveness (FOUR) scoring system are commonly used.[76] [77]

Glasgow Coma Scale (GCS)

The GCS is commonly used to grade the severity of the impairment of consciousness.[76] The FOUR scoring system evaluates additional neurological elements compared with the GCS, and appears to be equally reliable.[78] [The FOUR Score] (https://www.coma.uliege.be/severe-brain-injury) Additionally, the FOUR scoring system is applicable in intubated patients, patients unable to respond verbally, and in those patients with abnormal respiratory pattern.[76][78] Administering the FOUR score requires an experienced assessor and may take more time than the GCS.

Focused neurological examination

It is important to localize the anatomical-physiological site of the coma. Usually if the brainstem functions are preserved the site is more rostral or the brain has been affected in a diffuse manner that relatively spares the more resistant cranial nerve nuclei. However, there are some caveats. Some specific aspects of findings on neurological exam are worth noting.

Responsiveness

- Scoring systems that are more detailed than GCS are used in the ICU setting. For example, the FOUR scoring system includes eye movements, including tracking, and some motor responses (e.g., myoclonus) that are not captured by the GCS system.[77] [78]
- The motor response varies with the depth and severity of impairment of consciousness and the affected level of the neuraxis.
- A localizing response, for example toward an irritating stimulus, especially crossing the midline, indicates a lesser degree of impairment than posturing (decorticate or decerebrate) or no response.
- Visual tracking of a mirror that reflects back the image of the face or eyes of the patient differentiates a lighter degree of impaired consciousness from that of coma or vegetative state (UWS).[79]
- Patients with carbon monoxide poisoning usually have intact brainstem reflexes with impaired consciousness.

Pupillary reflexes

- Pupils may be unreactive in patients with hypothermia.
- Can be affected with drugs that have anticholinergic properties; for example, massive overdoses of tricyclic antidepressants.
- All brainstem reflexes, including pupillary responses, may be reversibly abolished with massive overdoses of barbiturates, profound hypoglycemia, or anoxic-ischemic encephalopathy. The reversibility of lost brain functions varies; these conditions can cause neuronal death if the insult is severe and prolonged.
- Pupils can be small but reactive in opioid intoxication.
- Pupils are initially small with central (diencephalic) herniation.
- Patients with basilar artery thrombosis may have pupillary palsies.
- Patients with concussion often undergo a transient impairment of brainstem function, including loss of pupillary and corneal reflexes.

The vestibular-ocular reflex (VOR)

- Tested with oculocephalic (quick turn of head from side to side or in the anterior-posterior plane) or oculovestibular (ice water injection into external ear canal) procedures. These procedures stimulate and test the integrity of the semicircular canals of the inner ear, and the brainstem connections linking the vestibular nuclei, gaze centers, and III and VI cranial nerve nuclei.
- May be impaired with herniation syndromes.
- Can be selectively impaired in Wernicke encephalopathy, without affecting pupillary or other cranial nerve reflexes. This happens because there is a selective involvement of gray matter structures adjacent to the ventricles and cerebral aqueduct in Wernicke encephalopathy; including the vestibular nuclei involved in the VOR.
- Large or cumulative doses of sedative drugs can selectively and transiently abolish the VOR.[80]
- Patients with basilar artery thrombosis may have ocular palsies.

- Not tested in trauma patients until cervical spine injuries have been ruled out.

Profound neuromuscular weakness

- Hypophosphatemia, when acute and profound, can be similar to Guillain-Barre syndrome. This can be seen in the refeeding syndrome, in which there is an increased shift of phosphate into cells after a glucose load in severely malnourished patients.[81]
- Flaccid quadriplegia is also sometimes a feature of acute, severe hypokalemia or hypomagnesemia.
- Patients with basilar artery thrombosis may have pseudobulbar palsy and/or quadriparesis.
- Patients with subfalcine herniation + diencephalic displacement may have associated signs of hemiparesis.
- Those with West Nile encephalitis may have bulbar paralysis and quadriplegia due to the involvement of motor neurons.
- In locked-in states, consciousness is preserved but motor output is impaired:
    - Basis pontis lesions: upper motor neuron palsy of lower cranial nerves (pseudobulbar palsy) and 4 limbs, vertical eye movement, eyes open and close voluntarily
    - Polyneuropathy: no vertical eye movement, may lose pupillary reflexes, absent deep tendon reflexes
    - Pharmacologic paralysis: intact pupillary reflexes.

Seizures

- Most commonly myoclonic (with bilaterally synchronous jerks, distinct from multifocal myoclonus), can occur in a number of metabolic encephalopathies, including hyponatremia, hyperosmolar states (especially in nonketotic hyperglycemia, where seizures can be misleadingly focal), hypocalcemia, extreme hypercalcemia, uremia, advanced hepatic encephalopathy, and hypoglycemia, and in postresuscitation encephalopathy after cardiac arrest. In the latter situation, myoclonic status epilepticus is often fatal, without recovery of awareness.[82] This is due to widespread neuronal death in a pattern that is very distinct from the pattern of neuronal loss after status epilepticus.[83]

Signs of herniation syndromes

- Subfalcine herniation may produce progressive impairment of consciousness with/without hemiparesis, and late oculomotor palsy.
- Uncal herniation may produce early oculomotor palsy before impaired consciousness.
- Central (diencephalic) herniation may produce initially small pupils and then impairment of consciousness, with late irreversible oculomotor palsy.
- Rostrocaudal herniation may produce abrupt loss of consciousness with cranial nerve palsies.
- Tonsillar herniation may produce respiratory arrest followed by hypertension, then hypotension, coma and often brain death.

Oculomotor signs associated with herniation include:

- Gaze preference or conjugate eye deviation to one side initially.
- Followed by pupillary asymmetry due to stretching of the third (oculomotor) cranial nerve over the clivus on the side of the mass.
- This usually manifests as dilation of the pupil ipsilateral to the lesion (note that about 20% of people have anisocoria). This is followed by loss of ipsilateral pupillary reactivity and paralysis of adduction of the eye.

- In later stages the opposite pupil loses its reactivity, due to intrinsic midbrain damage from herniation.

Laboratory investigations

Arterial or capillary blood gas determination can be very helpful in the presence of hyperventilation and occasionally in hypoventilation and for some toxidromes. ABG analysis is readily available and of some confirmatory value in psychogenic unresponsiveness. In pseudoseizures, blood gases are usually normal or may show a respiratory alkalosis from hyperventilation, as opposed to the profound, mixed metabolic-respiratory acidosis of a convulsive seizure. The correlation of basic respiratory patterns with blood gas determination can narrow the differential diagnostic possibilities considerably.

- Hyperventilation with metabolic acidosis: possible causes include uremia, diabetic ketoacidosis, lactic acidosis, or poisoning with salicylates, methanol, or ethylene glycol.
- Hyperventilation with respiratory alkalosis: possible causes include liver failure, acute sepsis, any cardiopulmonary state that causes hypoxemia, the acute phase of salicylate poisoning, or psychogenic hyperventilation.
- Hypoventilation with respiratory acidosis: coma occurs only if there is severe hypercapnia. Causes include respiratory failure due to either central or peripheral nerve disease, and chest conditions or deformities.
- Hypoventilation with metabolic alkalosis: consciousness is usually not impaired. Causes include vomiting and alkali ingestion, but psychogenic unresponsiveness or an additional cause should be suspected if the patient is unconscious.

Breathing Pattern	Metabolic Pattern	pH, PaCO2, HCO3	Specific Conditions
Hyperventilation	Metabolic acidosis	pH <7.3, PaCO2 <30 mmHg, HCO3 <17 mmol/L	Uremia, diabetic ketoacidosis, lactic acidosis, salicylates, methanol, ethylene glycol
Hyperventilation	Respiratory Alkalosis	pH>7.45, PaCO2 <30 mmHg, HCO3 >17 mmol/L	Hepatic failure, acute sepsis, acute salicylate intoxication, cardiopulmonary states with hypoxemia, psychogenic causes
Hypoventilation	Respiratory acidosis	pH <7.35 (if acute), PaCO2 > 90 mmHg, HCO3 >17 mmol/L	Respiratory failure from central (e.g., brain or spinal cord) or peripheral nervous system disease, chest conditions or deformities. Coma only with severe hypercarbia.
Hypoventilation	Metabolic alkalosis	pH> 7.45, PaCO2 >45 mm Hg, HCO3 >30 mmol/L	Vomiting, alkali ingestion. Usually no impairment of consciousness; if so, suspect psychogenic unresponsiveness or additional cause.

Respiratory abnormalities, blood gas determination, and diagnostic possibilities

Table created by G. Bryan Young, MD; used with permission

Serum glucose, calcium, sodium, potassium, magnesium, phosphate, urea, and creatinine should be checked to evaluate the cause of syncope, fainting, or seizure and to assess for the presence of electrolyte disorders.

Once the differential has been narrowed, further laboratory tests can be performed according to the suspected cause.

- Liver function tests should be done if hepatic failure is suspected.
- International normalized ratio (INR) is sensitive to acute hepatocellular failure.
- "Drug screen" is rarely comprehensive but can be specified to include alcohol, benzodiazepines, barbiturates, opioids, cocaine, amphetamines, tricyclic antidepressants, salicylates, acetaminophen, and other agents. Some drugs, such as antihistamines, may not have an available assay and one must go on clinical suspicions.
- Blood cultures should be done in the presence of fever or hypothermia.

- Blood carboxyhemoglobin level is required if carbon monoxide poisoning is suspected, bearing in mind that smokers may have slightly elevated levels.
- Pyruvate and serum thiamine should be measured if Wernicke encephalopathy is suspected.
- Specific drug or metabolic assays can be done in special circumstances.

Imaging

Imaging is essential when there is a strong possibility of a structural brain lesion or for diagnosing specific disorders. A CT head scan is most commonly used, as it is quick, available, and requires less preparation than an MRI scan; however, MRI can provide more detail. Consensus recommendations from the American College of Radiology support noncontrast CT for adult patients with new unexplained altered mental status and suspected intracranial pathology or focal neurologic deficit.[84]

CT is sensitive to intracranial hemorrhages, major shifts of midline structures, and mass effect. Patients with mass lesions (e.g., brain abscess, tumor, intracerebral hemorrhage, trauma with intracerebral or extracerebral hematoma) and herniation syndrome require urgent imaging. An unenhanced CT is usually performed first, then contrast CT if necessary to clarify the nature of mass (e.g., differentiating tumor from brain abscess).

MRI is usually performed later and can be helpful in showing multiple lesions (e.g., metastases) and their nature (e.g., infarctions vs inflammatory or neoplastic lesions).

Focal signs, such as a hemiparesis or an oculomotor palsy in a comatose patient, should also prompt a scan. However, coma may precede such focal signs in patients with supratentorial mass lesions. Thus, neuroimaging is also indicated when structural lesions are possible or if the diagnosis is uncertain.

Imaging in patients with traumatic brain injury and suspected intracranial injury

Consensus recommendations from the American College of Radiology support noncontrast CT use as a first-line imaging modality in patients with traumatic brain injury.[85]

Key recommendations from the National Institute for Health and Care Excellence (NICE) guideline for head injury management:[17]

- Refer to neurosurgical center if any of the following are present:
    - Persisting coma: GCS score 8/15 or less after initial resuscitation
    - Unexplained confusion that persists for more than 4 hours
    - Deterioration in level of consciousness after admission
    - Progressive focal neurologic signs
    - A seizure without full recovery
    - Definite or suspected penetrating injury
    - Cerebrospinal fluid (CSF) leak.

For people aged 16 years and over, a CT head scan is needed within 1 hour if any of the following is present:[17]

-
    - GCS of 12 or less on initial assessment in the emergency department
    - GCS less than 15 at 2 hours after the injury

- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle sign)
- Post-traumatic seizure
- Focal neurological deficit
- More than one episode of vomiting

- For people aged 16 years and over who have had some loss of consciousness or amnesia since the injury, CT head should be performed within 8 hours (or within the hour in someone presenting more than 8 hours after the injury) if any of the following are present:[17]

  - Age 65 years or older
  - Any history of bleeding or clotting disorders
  - Dangerous mechanism of injury (e.g., a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle, or fall from a height greater than 1 meter or 5 stairs)
  - More than 30 minutes retrograde amnesia of events immediately before the head injury

For people under 16 years who have sustained a head injury, CT head should be performed within 1 hour of any of the following risk factors being identified:[17]

- Suspicion of nonaccidental injury
- Posttraumatic seizure
- On initial emergency department assessment, a GCS score <14 or, for infants under 1 year, a GCS score (pediatric) <15
- At 2 hours after the injury, a GCS score <15
- Suspected open or depressed skull fracture, or tense fontanel
- Any sign of basal skull fracture (hemotympanum, "panda" eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign)
- Focal neurologic deficit
- For infants under 1 year, a bruise, swelling, or laceration of more than 5 cm on the head.

For people under 16 years who have sustained a head injury and have more than one of these risk factors, CT head should be performed within 1 hour of the risk factors being identified:[17]

- Loss of consciousness lasting more than 5 minutes (witnessed)
- Abnormal drowsiness
- 3 or more discrete episodes of vomiting
- Dangerous mechanism of injury (high-speed road traffic accident as a pedestrian, cyclist or vehicle occupant, fall from a height of more than 3 metres, high-speed injury from a projectile or other object)
- Amnesia (anterograde or retrograde) lasting more than 5 minutes (it is not possible to assess amnesia in children who are preverbal and is unlikely to be possible in children under 5)
- Any current bleeding or clotting disorder.

People under 16 years who have sustained a head injury but have only one of the above risk factors (beginning Loss of consciousness lasting more than 5 minutes [witnessed]) should be observed for a minimum of 4 hours in a hospital. If, during observation, any of the following risk factors are identified, CT head should be performed within 1 hour:[17]

- A GCS score <15
- Further vomiting

- A further episode of abnormal drowsiness.

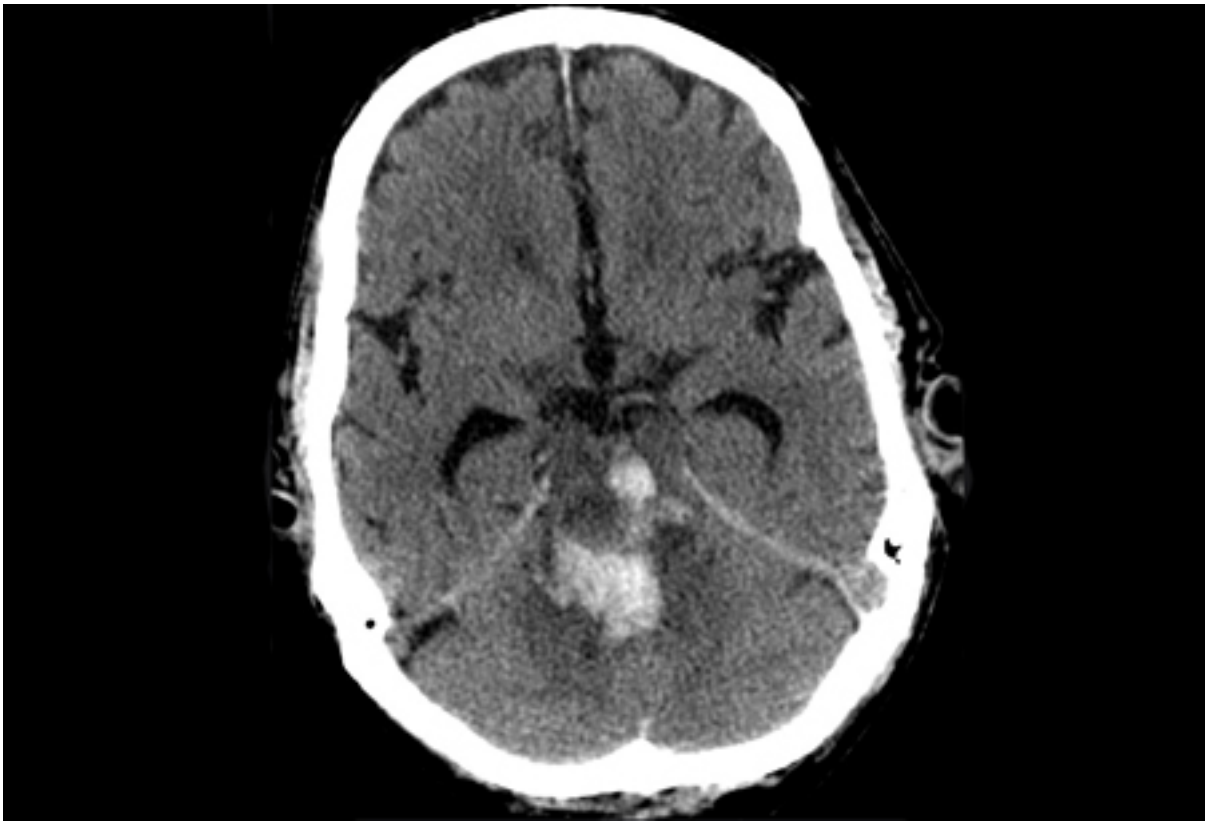
If none of these risk factors occur during observation, clinical judgement should be used to determine whether a longer period of observation is needed.[17]

Imaging in anticoagulated patients

Several guidelines recommend, or suggest consideration of, CT head imaging for anticoagulated patients after minor head injury, regardless of symptoms.[17][86] [87]

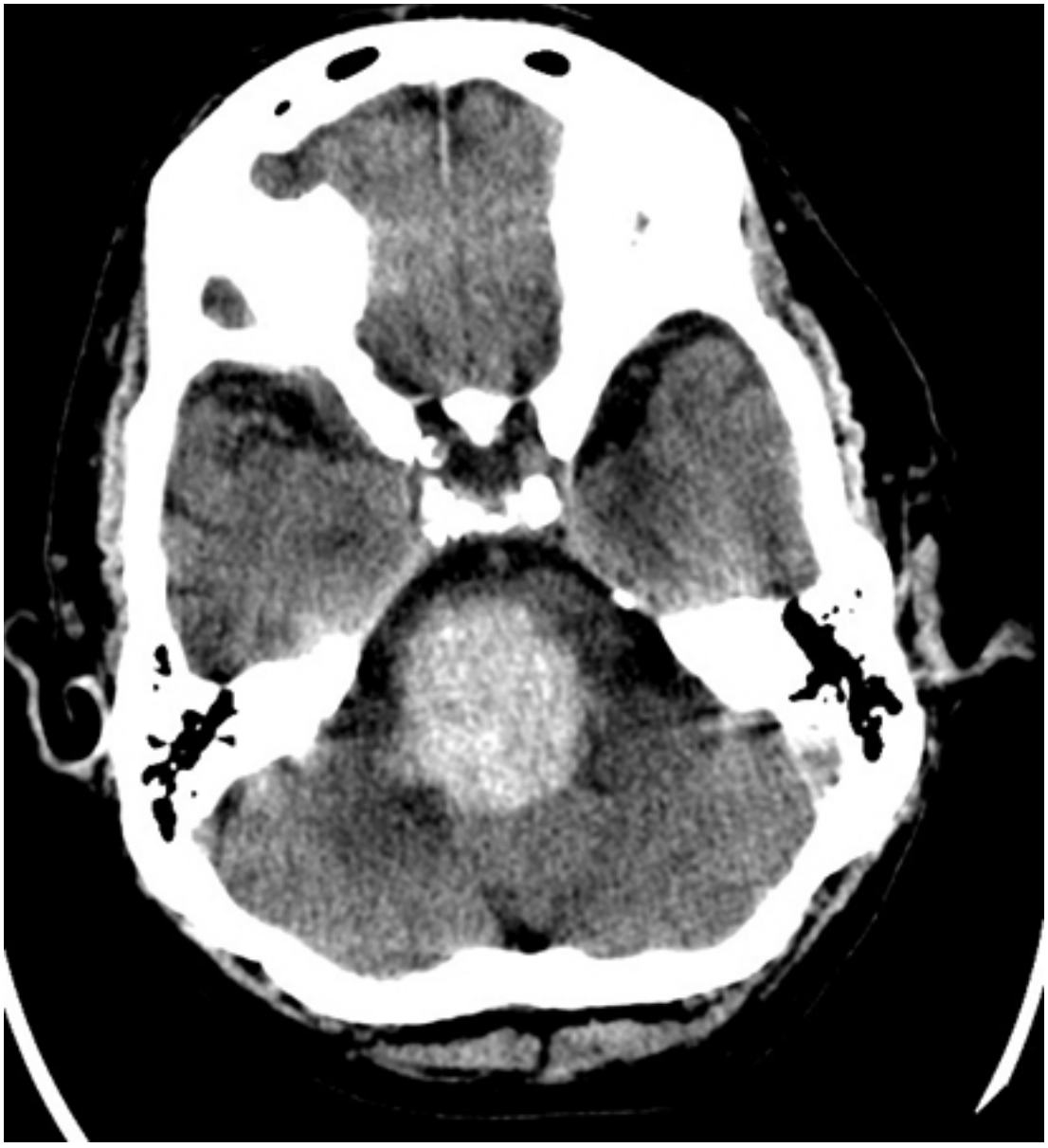
NICE recommends consideration of a CT head scan for those with a head injury who are taking an anticoagulant or antiplatelet medication (and have no other indication for a CT head scan):[17]

- within 8 hours of the injury
- within the hour if they present more than 8 hours after the injury.



Brainstem hemorrhage in the midbrain that extended from a hypertensive hemorrhage in the pons

From the personal collection of G. Bryan Young, MD; used with permission



Hypertensive hemorrhage in the pons that ruptured into the fourth ventricle and extended into the midbrain

From the personal collection of G. Bryan Young, MD; used with permission

Lumbar puncture and CSF analysis

Lumbar puncture is indicated if there is suspicion of meningitis, especially bacterial, fungal, or tuberculous, and for detecting meningeal cancer. Lumbar puncture can also confirm SAH from a ruptured aneurysm when CT has not detected it (5% of cases). Xanthochromia, a yellow staining of the CSF from hemoglobin breakdown products, can be suspected clinically and confirmed by spectrophotometry.

More specific diagnostic testing, apart from culture, stains, cytology, and flow cytometry, includes:

- polymerase chain reaction (PCR) for herpes simplex virus (HSV) 1 and 2
- broad-range bacterial PCR
- specific meningeal pathogen PCR
- PCR for *Mycobacterium tuberculosis*

- reverse transcriptase (RT) PCR for enteroviruses
- PCR for West Nile virus
- PCR for Epstein-Barr virus
- PCR for varicella zoster virus
- PCR for cytomegalovirus DNA
- PCR for HIV RNA
- RT-PCR for rabies virus.

Antigen screening can be done for cryptococcal and histoplasma polysaccharide antigens. Antibody screens in the CSF are available for HSV (serum-to-CSF antibody ratio of <20:1), arthropod-borne viruses, *Borrelia burgdorferi* (for suspected Lyme disease), and rabies virus; complement fixation antibody testing for *Coccidioides immitis* can also be performed. CSF analysis may also help in the diagnosis of acute inflammatory demyelinative polyneuropathy (in cases of locked-in state).

EEG

EEG can be of great help in detecting seizures; it seems appropriate to request one, even in the ER, when the cause of coma is not apparent and brainstem reflexes are intact. Evidence suggests that at least 14% of patients who did not wake after a convulsive seizure were in nonconvulsive status epilepticus (NCSE).[88]

Seizures may also be acquired in the ICU, especially in those with structural brain lesions. It has been demonstrated that at least 8% of patients comatose from brain injury are in NCSE.[35] [89] Most often this is undetectable without EEG. Because status epilepticus can damage the brain, it is important that seizures be detected early and treated promptly and effectively. The liberal use of EEG in the ICU is helpful; continuous monitoring for at least 72 hours increases NCSE diagnostic yield and, in patients with seizures, provides feedback that the seizures are controlled and that the sedation/anesthesia is not excessive.

EEG is also helpful for diagnosing pseudoseizures or psychogenic seizures (in patients with psychogenic unresponsiveness), acute herpes simplex encephalitis (sensitive in >80% of cases), hypothermia, hyperthermia, SAH, and inflammatory processes (e.g., burns).[24]

EEG demonstrates different patterns (e.g., slow pattern, burst-suppression pattern, isoelectric pattern). These features are not specific to etiology and are mainly used to grade the severity of the encephalopathy. The most profound abnormality is generalized suppression of voltage/electrocerebral silence, then a burst-suppression pattern. These are common in very severe cases of anoxic-ischemic encephalopathy after cardiac arrest, but they may be found in more reversible encephalopathies due to overdose of barbiturates, benzodiazepines, anesthetic agents, or profound hypothermia. Diffuse slowing with rhythmic waves or triphasic waves indicates a somewhat less severe but still profound encephalopathy, usually but not invariably due to metabolic derangements: for example, uremia, hepatic failure, or sepsis.

Electromyography (EMG)

In cases of unresponsiveness, EMG can help exclude a neuromuscular cause. For example, neuromuscular blockade from the prolonged action of muscle relaxants and profound, diffuse polyneuropathies (e.g., acute inflammatory demyelinative polyneuropathy and the axonal form of Guillain-Barre syndrome).

Prognostic tests

The prognosis of patients with severe diffuse axonal injury (DAI) can be estimated using:

- Somatosensory evoked response testing, which uses a single sensory pathway and has been shown to be sensitive and specific
- Magnetic transcranial cortical motor stimulation, which can be used to assess the corticospinal motor integrity, although this use has not yet been standardized[90]
- Diffusion tensor imaging, which offers promising prognostic strategy, especially when used in combination with somatosensory evoked responses[91]
- Metabolic studies, which demonstrate glucose uptake and metabolism in gray and white matter of the brain using positron emission tomography (PET) scanning, may be clinically useful, but this is yet to be determined.[92] [93]

The prognosis of patients with anoxic-ischemic encephalopathy after cardiac arrest can be estimated using:

- Somatosensory evoked response testing, which shows bilateral absence of the N20 response (from the primary sensory cortex) to median nerve stimulation of the wrist[94]
- Serum neuronal specific enolase >33 micrograms/L between days 1 and 3 reliably predicts an outcome no better than severe disability requiring long-term nursing home care.[95]

The prognosis of patients with carbon monoxide poisoning may be estimated using:

- Single-photon emission CT during the later stages.

The prognosis of patients in coma is often difficult. However, some advances have been made in the application of ancillary testing:

- Somatosensory evoked potential holds promise in both children and adults[96] [97]
- Diffusion tensor imaging (DTI) allows for the evaluation of fiber tracts, taking advantage of the anisotropic motion of water within the axons (fractional anisotropy). Studies of mild traumatic brain injuries have shown abnormalities in the genu of the corpus callosum. DTI is beginning to be used clinically in traumatic brain injuries.[98]

Differentials overview

Common
Stroke
Cardiac arrest
Hypertensive encephalopathy
Basilar artery thrombosis
Cerebral venous thrombosis
Alcohol-use disorder
Substance abuse and overdose
Carbon monoxide poisoning
Sepsis-associated encephalopathy
Bacterial meningitis
Syncope
Seizure disorder
Traumatic brain injury
Hypoglycemia
Hyperglycemia
Hepatic encephalopathy
Hyponatremia
Hypothyroidism
Wernicke encephalopathy
Hypophosphatemia

Uncommon

- Subarachnoid hemorrhage
- Encephalitis
- Brain abscess
- Brain tumor
- Hypernatremia
- Hypercalcemia
- Hypocalcemia
- Hypermagnesemia
- Hypomagnesemia
- Porphyria
- Mitochondrial disorder
- Thyroid storm
- Burns
- Hyperthermia
- Hypothermia
- Psychogenic unresponsiveness
- Locked-in state

Differentials

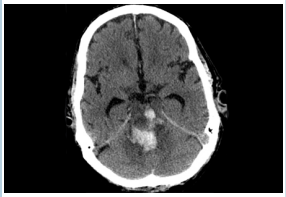
Common

Stroke

History	Exam	1st Test	Other tests
transient/permanent symptoms: usually abrupt onset, numbness, paresthesia, weakness, paralysis, headache, facial drop, speech disturbance, swallowing difficulties, vision loss, memory loss, and/or loss of consciousness; mass effect/herniation: usually progressive impairment of consciousness, one-sided weakness, visual disturbance, hearing disturbance, taste disturbance, difficulty swallowing, facial paralysis, and/or difficulty breathing	commonly: hypertension, contralateral hemiparesis, hemisensory loss, dysphasia, dysphagia, anosognosia, visuospatial deficit, contralateral vision loss, memory loss, Weber syndrome (ipsilateral ocular nerve palsy and contralateral hemiplegia), constricted pupils, and/or ipsilateral ataxia followed by ipsilateral gaze paresis and ipsilateral facial paralysis; mass effect/herniation: usually progressive impairment of consciousness, hemiparesis, oculomotor palsy, cranial nerve palsies, respiratory arrest, hypertension, hypotension, and/or brain death	»**CT head:** hemorrhagic: intra- or extracerebral mass effect with displacement of midline structures (septum pellucidum or pineal by >9 mm from the midline); ischemic: hypoattenuation (darkness) of the brain parenchyma, loss of gray matter-white matter differentiation, sulcal effacement CT is usually more readily available and faster than MRI, but it may provide less detail. Unenhanced scans are performed first, then contrast is added if needed to clarify nature of mass (e.g., differentiation from tumor or brain abscess).	»**MRI brain:** hemorrhagic: aneurysm or arteriovenous malformation; ischemic: brightness on diffuse weighted imaging, increased signal in the ischemic territory on T2 images Usually performed later. MRI can provide more detail than CT. Can be helpful in showing the vascular supply to a vascular malformation that has bled. »**echo:** normal, valvular disease, or dilated cardiac chamber »**blood cultures:** normal, bacteremia, or fungemia With infective endocarditis, systemic embolization may occur and cause ischemic stroke.

Common

Stroke

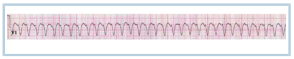
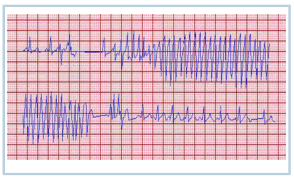
History	Exam	1st Test	Other tests
		 *Brainstem hemorrhage in the midbrain that extended from a hypertensive hemorrhage in the pons* *From the personal collection of G. Bryan Young, MD; used with permission* »**ECG:** normal, myocardial infarction (MI)-related changes, or atrial fibrillation (AF) Post-MI cardiac emboli may cause ischemic stroke. AF may produce cardiac emboli that may cause ischemic stroke. Patients with AF may be taking warfarin, which increases the risk of hemorrhagic stroke.	

Cardiac arrest

History	Exam	1st Test	Other tests
sudden collapse, may be preceded by chest pain	absent carotid pulse	»**ECG:** cardiac rhythm disturbance: for example, ventricular fibrillation or asystole	»**ABG:** may show respiratory acidosis; metabolic acidosis; respiratory acidosis with renal

Common

Cardiac arrest

History	Exam	1st Test	Other tests
		Cardioversion with electrical shocks may be indicated. Intravenous epinephrine is required for asystole.  *Monomorphic ventricular tachycardia* *From the collection of Amar Krishnaswamy; used with permission*  *Torsades de pointes* *From the collection of Amar Krishnaswamy; used with permission*	compensation; metabolic acidosis with respiratory compensation; mixed metabolic and respiratory acidosis »**somatosensory evoked responses with median nerve stimulation at the wrist:** variable This is performed between 1 and 3 days postarrest or later. Bilateral absent cerebral cortical response (N20) indicates very poor prognosis (almost always in vegetative state [unresponsive wakefulness syndrome] or severe disability). The false-positive rate very close to zero. »**neuron-specific enolase:** variable Serum test done at 1-3 days postarrest. Values >33 micrograms/L are associated with poor prognosis. Test availability may vary by region.

Hypertensive encephalopathy

History	Exam	1st Test	Other tests
visual disturbance, impaired consciousness, weakness;	hypertension, variable focal features, for example, hemiplegia; posterior reversible	»**cranial CT:** normal or vasogenic edema, usually most marked in the white matter of the	»**MRI brain:** vasogenic edema, usually most marked in the white matter of the posterior

Common

Hypertensive encephalopathy

History	Exam	1st Test	Other tests
posterior reversible encephalopathy syndrome: vision loss, convulsive seizures	encephalopathy syndrome: cortical blindness (pupillary light reflex is spared but patient is blind)	posterior parts of the cerebral hemispheres Caused by acute/ subacute elevations of blood pressure to levels that overcome cerebral autoregulation. An apparent diffusion coefficient (ADC) map should be done to exclude infarction.	parts of the cerebral hemispheres Performed if CT negative and condition not improving. »**BUN:** elevated serum urea Often caused by accelerated hypertension. Performed secondary to imaging, but still important. »**creatinine:** elevated serum creatinine Often caused by accelerated hypertension. Performed secondary to imaging, but still important. »**urine dipstick:** proteinuria Often caused by accelerated hypertension. Performed secondary to imaging, but still important.

Basilar artery thrombosis

History	Exam	1st Test	Other tests
commonly vision loss and photopsia	often quadriparesis, pseudobulbar palsy, papillary and ocular palsies	»**cranial CT with CT angiogram:** basilar artery occlusion Occlusion is seen either in the proximal portion (feature of basilar syndrome, usually with	»**MRI brain:** basilar artery occlusion; brainstem ischemia; thalamus ischemia, ischemia of peripheral posterior cerebral artery territories

Common

Basilar artery thrombosis

History	Exam	1st Test	Other tests
		midbrain and thalamic damage) or more extensively. CT is more easily obtained and gives better detail than MRI.	Occlusion is seen either in the proximal portion (feature of basilar syndrome, usually with midbrain and thalamic damage) or more extensively. MRI can be helpful in showing the vascular supply to a vascular malformation that has bled.

Cerebral venous thrombosis

History	Exam	1st Test	Other tests
intractable worsening headache of subacute onset, often associated with nausea and vomiting, seizures common	papilledema; venous infarction: focal neurology, for example, hemiplegia	»**MRI brain with venous phase:** occluded cortical veins or larger venous channels, often parenchymal hemorrhages An accurate diagnosis, shown by CT or magnetic resonance venography is needed promptly. MRI can provide more detail than CT. Can be helpful in showing the vascular supply to a vascular malformation that has bled. »**CT angiogram with venous follow through:** occluded cortical veins or deep or superficial venous channels	»**thrombophilia screen:** normal, protein C deficiency, protein S deficiency, factor V Leiden, antithrombin 3 deficiency, polycythemia, thrombocytosis, paroxysmal nocturnal hemoglobinuria More than one third of cases are due to a coagulation disorder. This is done secondary to acute neuroimaging and anticoagulation. However, it is important to allow prophylaxis against further episodes/relapses.

Common

Alcohol-use#disorder

History	Exam	1st Test	Other tests
history of harmful use of alcohol and alcohol dependence; tolerance; withdrawal; impaired control of drinking behavior; continued alcohol use despite adverse consequences	odor of alcoholic beverage on breath, stigmata of liver disease in chronic alcoholics	»**serum ethanol:** >80 mg/dL	

Substance abuse and overdose

History	Exam	1st Test	Other tests
ingestion of lysergic acid diethylamide (LSD), cocaine, amphetamines, opioids, sedatives, organophosphates, carbamate insecticides, jimson weed, deadly nightshade, methanol, ethylene glycol (antifreeze), ephedrine, pseudoephedrine, alpha-2 agonists, sedatives, first-generation antihistamines, tricyclic antidepressants, benztropine	variable	»**drug screen:** positive for toxin Rarely comprehensive but can be specified to include alcohol, benzodiazepines, barbiturates, opioids, cocaine, amphetamines, tricyclic antidepressants, salicylates, acetaminophen, and other agents. Some drugs, for example, antihistamines, may not have an available assay and one must go on clinical suspicion.	»**ABG:** normal, respiratory alkalosis, or metabolic acidosis Respiratory alkalosis may be present with acute salicylate intoxication. Metabolic acidosis may be present with salicylate, methanol, ethylene glycol ingestion.

Carbon monoxide poisoning

History	Exam	1st Test	Other tests
typically presents in winter months with headache, confusion, and abdominal discomfort; patients may visit the emergency room repeatedly with these	typically impaired consciousness with intact brainstem reflexes; cherry red discoloration of mucous membranes and lips is helpful but rarely	»**blood carboxyhemoglobin concentration:** >15% Smokers may have slightly elevated carbon monoxide (<15%).	»**MRI brain:** acute changes in white matter »**single-photon emission CT:** abnormally reduced metabolic activity

Common

Carbon monoxide poisoning

History	Exam	1st Test	Other tests
symptoms only to arrive later in coma; also presents as patients discovered comatose following exposure to internal combustion engine exhaust (vehicle or generator)	present (should not be relied on)		Performed for prognostic purposes.

Sepsis-associated encephalopathy

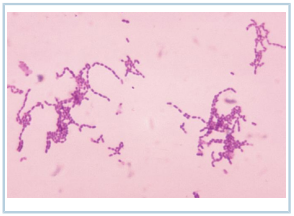
History	Exam	1st Test	Other tests
fever may be present; may be a history of confusion, delirium, and (commonly) any of: cough, shortness of breath, chest pain, dysuria, urinary urgency, urinary frequency, reduced urine output, loin pain, joint pain; may be history of risk factors such as recent surgery, presence of immunosuppression	elevated/depressed body temperature, increased heart rate, tachypnea; may be signs of local infection (e.g., abnormal chest examination), impaired attention, disorientation, delusions, hallucinations (delirium or stupor with paratonic rigidity or asterixis may precede coma); neurologic exam is otherwise normal, although cases in the intensive care unit (ICU) may develop a neuromyopathy (ICU-acquired weakness)	»**basic test panel (CBC, serum electrolytes, blood glucose, serum liver function tests, coagulation profile):** elevated WBC count or leukopenia; elevated urea and creatinine; low platelets; blood glucose may be elevated or, more rarely, low; serum transaminases and serum bilirubin may be elevated; may be prolonged or elevated INR, PT, aPTT If shock is present, urgent simultaneous treatment is required. WBC count may be normal in early stages of infection or in older patients. »**cultures and Gram stain of blood, urine, sputum, and body fluid:** responsible organisms may be identified »**arterial blood gas:** may be hypoxia, hypercapnia, elevated	»**EEG:** graded pattern of severity ranging from mild slowing to a burst-suppression pattern Findings are not specific and can be found in other metabolic encephalopathies; the severity of the EEG abnormality reflects the severity of sepsis.

Common

Sepsis-associated encephalopathy

History	Exam	1st Test	Other tests
		anion gap, metabolic acidosis »**serum lactate:** may be elevated >18 mg/dL (>2 mmol/L) May be possible to measure lactate in the arterial blood gas sample. »**ECG:** normal; may demonstrate tachycardia	

Bacterial meningitis

History	Exam	1st Test	Other tests
presence of any 2 of: fever, headache, neck stiffness, or any alteration in mental status before coma can suggest diagnosis; children also often have vomiting, photophobia, and lethargy	fever, ill appearance; meningococcal meningitis: petechial rash plus or minus shock, neck stiffness to forward flexion, inability to completely extend the lower limbs (Kernig sign), flexion at the hip and knee when the neck is flexed (Brudzinski sign)	»**CBC:** elevated WBC count with left shift »**blood culture:** positive for *Neisseria meningitidis* , *Streptococcus pneumoniae* , or *Haemophilus influenzae* in 40% to 60% of cases Often negative if patient has received earlier antibiotics.  *Photomicrograph of Gram-stained Streptococcus species bacteria* *From the CDC Public Health Image Library*	

Common

Bacterial meningitis

History	Exam	1st Test	Other tests
		»**CT or MRI brain:** normal or early hydrocephalus and meningeal enhancement Blood cultures and initiation of treatment with empirical antibiotics is important while requesting neuroimaging. »**cerebrospinal fluid (CSF) analysis:** elevated CSF pressure (usually >180 mm H_2O or >20 mmHg), pleocytosis (usually >1000 WBCs), mostly polymorphonuclear leukocytes, elevated protein (>45 mg/dL, reduced glucose (usually <40 mg/L or 3 mmol/L and <40% of serum glucose); CSF Gram stain positive in most untreated cases Neuroimaging must be negative for mass effect.	

◊ Syncope

History	Exam	1st Test	Other tests
transient coma; prodromal diaphoresis, nausea, dimming of vision, tinnitus; may be precipitated by upright posture, fainting avoided by sitting or lying down; coma may be abrupt without postural influence; convulsions/ incontinence may	postural hypotension: drop in blood pressure from supine to standing; arrhythmia/ pulmonary embolism/ cardiac cause: abnormal pulse rate/ rhythm, murmurs; neurological cause: sensory, motor, speech, vision deficits; carotid hypersensitivity: carotid	»**CBC:** anemic cause: reduced Hb; infective cause: elevated WBC count »**serum glucose:** metabolic cause: elevated or reduced »**ECG:** abnormal results may demonstrate cardiac cause	»**exercise stress test:** abnormal results may demonstrate cardiac cause »**tilt table test:** abnormal results may demonstrate cardiac cause or reflex fainting (vasomotor or vasodepressor syncope)

Common

◊ Syncope

History	Exam	1st Test	Other tests
occur; usually abruptly regain consciousness/ orientation	sinus massage may reproduce symptoms	It may be necessary to monitor patients for ≥24 hours to detect intermittent arrhythmias. There may be evidence of heart block of various degrees, which can be a clue for intermittent complete heart block causing syncope.	This can be helpful in cases of frequent syncope. It is fairly reliable if positive. »**EEG:** abnormal results may demonstrate neurologic cause »**CT head:** abnormal results may demonstrate neurologic cause »**MRI brain:** abnormal results may demonstrate neurologic cause

Seizure disorder

History	Exam	1st Test	Other tests
transient coma; prodromal symptoms including diaphoresis, nausea, dimming of vision, and tinnitus; convulsive movements and incontinence can occur; usually followed by confusion and drowsiness that often lasts ≥10 minutes	convulsive: bilateral synchronous convulsions, open eyes; nonconvulsive: no convulsions, infrequently nystagmoid eye movements, or bilateral facial twitching	»**EEG:** generalized seizure activity Seizures are usually generalized if the patient is comatose, but these are infrequently present; in most cases an EEG is needed for confirmation. Have a low threshold for ordering EEGs when the cause is not apparent. Risk factors include a preceding convulsive seizure followed by coma, past history of epilepsy, or a structural brain lesion. »**serum glucose:** normal, extreme hypoglycemia, or extreme hyperglycemia	»**MRI brain:** neoplastic, traumatic, vascular, inflammatory, or degenerative lesions may be present

Common

Seizure disorder

History	Exam	1st Test	Other tests
		Can be useful in determining the cause of unexplained seizures. Extreme hypoglycemia or hyperglycemia can cause provoked generalized or partial seizures. »**electrolyte panel:** normal, hyponatremia, hypernatremia, magnesium abnormality, calcium abnormality, or phosphate abnormality »**BUN:** normal or uremia Uremia can cause provoked generalized or partial seizures. »**serum creatine kinase:** normal or markedly elevated Elevated levels can indicate the risk of myoglobinuria and renal damage. »**serum antiepileptic drug levels:** normal or low This is done for patients with known seizure disorders on antiseizure medications. Serum levels are usually very low in these patients. In special circumstances it is best to "load" the patient with their usual drug.	

Common

Seizure disorder

History	Exam	1st Test	Other tests
		»**drug screen:** normal, or positive for amphetamines/cocaine	

Traumatic brain injury

History	Exam	1st Test	Other tests
concussion: transient coma following blow to head, retrograde amnesia; "talk and die" syndrome: concussion followed by lucid interval then coma; diffuse axonal injury (DAI): instant coma, eye opening usually after 2 to 3 weeks, awareness recovery variable; mass effect/ herniation: usually progressive impairment of consciousness, one-sided weakness, visual disturbance, hearing disturbance, taste disturbance, difficulty swallowing, facial paralysis, and/or difficulty breathing	concussion: transient apnea, loss of pupillary reflexes, loss of corneal reflexes; mass effect/herniation from epidural/subdural hematoma: usually progressive impairment of consciousness, hemiparesis, oculomotor palsy, cranial nerve palsies, respiratory arrest, hypertension, hypotension, and/or brain death	»**CT head:** mass lesion: intra- or extracerebral mass effect with displacement of midline structures (septum pellucidum or pineal by >9 mm from the midline), petechial hemorrhages in cerebral white matter; DAI: petechial hemorrhages in corpus callosum and dorsolateral brainstem CT is usually more readily available and faster than MRI, but it may provide less detail. For mass lesions, unenhanced scans are performed first and then contrast is added if needed to clarify the nature of the mass. Neuroradiological confirmation of DAI is more problematic, as the axons cannot be visualized.	»**skull x-ray:** may show linear or depressed skull fracture Only performed if CT is not available. »**MRI brain:** DAI: petechial hemorrhages; severe DAI: corpus callosum hemorrhage, dorsolateral rostral brainstem hemorrhage; mass lesion: extra-axial epidural or subdural hematomas, or intra-axial contusion with variable confluence (typically on orbital surfaces of frontal lobes, and in temporal lobe) Usually performed later. For mass lesions, MRI can provide more detail than CT. Neuroradiological confirmation of DAI is more problematic, as the axons cannot be visualized, although it is more sensitive for DAI than CT. »**tensor tract imaging:** DAI: tract damage Useful prognostic technique; shows tract

Common

Traumatic brain injury

History	Exam	1st Test	Other tests
			damage much better than conventional MRI. Availability may vary by region.[99] »**somatosensory evoked response testing:** DAI: bilateral absence or delay of the N20 response from median nerve stimulation Useful prognostic technique that uses a single sensory pathway. Usually shows a poor prognosis and dependency if the patient survives. Has been shown to be sensitive and specific for severe DAI.

Hypoglycemia

History	Exam	1st Test	Other tests
cold perspiration, confusion, multifocal or generalized seizures, lightheadedness, or agitation preceding loss of consciousness	increased heart rate, elevated blood pressure, diaphoresis	»**serum glucose:** reduced <2 mmol/L or 50 mg/dL	»**CT head:** normal »**MRI brain:** severe cases: increased diffusion weighted signal of cerebral cortex with thalamus and cerebellum sparing May be abnormal in severe cases and can be helpful prognostically.

Common

Hyperglycemia

History	Exam	1st Test	Other tests
increased diuresis, progressive confusion, history of diabetes mellitus, suboptimal insulin therapy, seizures	clinical dehydration, tachycardia, hypotension; diabetic ketoacidosis (DKA): Kussmaul breathing, acetone breath	»**serum glucose:** elevated May produce hyperosmolar state, with serum osmolality >320 mmol/L. »**urinary ketones:** normal or elevated if DKA »**serum ketones:** normal or elevated if DKA	»**ABG:** normal or metabolic acidosis if DKA »**CT head:** normal »**MRI brain:** normal

Hepatic encephalopathy

History	Exam	1st Test	Other tests
underlying hepatic failure, alcoholism, intravenous drug abuse, acetaminophen overdose; malaise, confusion/delirium, agitation, progressive impairment of consciousness from stupor to coma; chronic liver disease: decompensation often due to intercurrent infection, sedative drugs, excessive diuresis or constipation	ascites, spider nevi, dilated peri-umbilical veins, ± jaundice, tremor, increased tone, asterixis, Kaiser-Fleischer rings (crescentic, rusty brown discoloration in the limbus of the corneae, especially in young patients)	»**liver function tests (LFTs):** abnormal Bilirubin is usually elevated and aspartate aminotransferas is markedly elevated in hepatitis or acute liver failure. Plasma ammonia is usually elevated but is not helpful in its correlation with the degree of encephalopathy. »**INR:** normal or elevated Elevated when synthetic function of the liver is compromised. INR is useful in following the trend of worsening or improving liver function. »**serum glucose:** normal or reduced	

Common

Hepatic encephalopathy

History	Exam	1st Test	Other tests
		May be depressed in advanced liver failure. It is an index of the severity of acute liver failure. »**serum lactate:** normal or elevated Elevated in severe, acute liver failure. An index of severity of acute liver failure. »**CBC:** elevated WBC count if intercurrent infection »**serum electrolyte panel:** hyponatremia »**BUN:** elevated in cases with hepatorenal syndrome »**serum creatinine:** elevated in cases with hepatorenal syndrome »**ABG:** respiratory alkalosis	

Hyponatremia

History	Exam	1st Test	Other tests
headache, behavioral changes, nausea, vomiting, impaired consciousness	generalized or focal neurological impairment; occasionally mono- or hemiparesis, ataxia	»**serum electrolyte panel:** sodium reduced <145 mmol (145 mEq/L) Usually no clinical features unless serum sodium <125 mmol/L (125 mEq/L), especially for acute hyponatremia. Chronic hyponatremia is often well tolerated.	»**CT head:** normal or slight reduction in brain volume »**MRI brain:** normal

Common

Hypothyroidism

History	Exam	1st Test	Other tests
gradual slowing down to impairment of consciousness; weight gain, constipation, lethargy; precipitation by intercurrent infection, cold exposure, stress, phenytoin, amiodarone, lithium, or withdrawal of thyroid replacement therapy; myxedema coma: puffy eyes, previous thyroid disorder, head injury, or pituitary injury	myxedema coma: pale doughy skin, periorbital swelling, swollen tongue, hypothermia, bradycardia, slow relaxation phase of deep tendon reflexes, hypoventilation	»**thyroid function test (TFT):** reduced thyroxine, elevated or reduced thyroid-stimulating hormone (TSH) TSH is elevated with thyroid gland failure and is reduced in central nervous system (CNS; hypothalamic or pituitary) causes.	»**ABG:** elevated $PaCO_2$ Mild respiratory failure. »**EEG:** suppression of voltage and slowing of background rhythms Not specific but helpful feature. »**CT head:** normal or pituitary/hypothalamic lesion »**MRI brain:** normal or pituitary/hypothalamic lesion

Wernicke encephalopathy

History	Exam	1st Test	Other tests
coma, hypothermia; history of chronic alcohol misuse, malnutrition, gastric stapling, or patients requiring hemodialysis (not taking supplemental B vitamins)	absent vestibulo-ocular reflexes in hypothermic patient with preserved pupillary reflexes is a major clue; triad of ataxia, ophthalmoplegia, and encephalopathy is not always present	»**plasma pyruvate:** elevated Elevated with reduced pyruvate dehydrogenase. Reference range: 6-17 micromols/L or (0.5-1.5 mg/dL).	»**MRI brain:** increased signal on fluid-attenuated inversion recovery (FLAIR) in mammillary bodies, hypothalamus, medial thalamus, and floor of fourth ventricle Diagnosis is primarily clinical. MRI confirmation should not delay thiamine administration. »**blood#thiamine:** reduced Reference range is wide; useful in good labs with tight controls; it is often impractical as it is not readily available. »**erythrocyte transketolase:** reduced

Common

Wernicke encephalopathy

History	Exam	1st Test	Other tests
			Specific but seldom available.

Hypophosphatemia

History	Exam	1st Test	Other tests
previous malnutrition with recent in-hospital feeding; deterioration with stupor, coma, myoclonus, seizures, or profound weakness after being given nutritional supplementation or glucose solutions in the hospital	severe muscle weakness, features of metabolic encephalopathy, including multifocal myoclonus or seizures	»**serum phosphate:** reduced <1.5 mg/dL or 0.5 mmol/L Serum concentrations may fall precipitously after refeeding, as there is an increased shift of phosphate into cells. »**serum electrolyte panel:** normal or reduced magnesium, normal or reduced potassium	»**CT head:** normal

Uncommon

Subarachnoid hemorrhage

History	Exam	1st Test	Other tests
initial severe headache, described as "worst ever;" photophobia, neck stiffness, abrupt loss of consciousness in 30%; mass effect/ herniation: usually progressive impairment of consciousness, one-sided weakness, visual disturbance, hearing disturbance, taste disturbance, difficulty swallowing, facial paralysis, and/or difficulty breathing	neck stiffness to forward flexion (if not comatose); retinal or preretinal (subhyaloid) hemorrhage on funduscopy; early third nerve palsy may be present; mass effect/ herniation: usually progressive impairment of consciousness, hemiparesis, oculomotor palsy, cranial nerve palsies, respiratory arrest, hypertension, hypotension, and/or brain death	»**CT head:** blood in basal cisterns and subarachnoid space over the hemispheres (95% cases); intraventricular blood and early hydrocephalus (some cases) CT is highly sensitive if done in the first day or two, but lumbar puncture is needed if subarachnoid hemorrhage is still	»**CSF exam:** uniformly blood-tinged fluid with no "fall off" of red blood cell count comparing first and fourth tubes; may see xanthochromia »**CT angiogram:** aneurismal source of hemorrhage Preferred diagnostic test. Probably better than magnetic resonance angiography for detection of aneurysms. May be substituted for or

Uncommon

Subarachnoid hemorrhage

History	Exam	1st Test	Other tests
		possible and the CT is negative.	precede CSF analysis. Could be used as 2nd test if history and findings are strongly suggestive. Reveals the source of subarachnoid hemorrhage >95% of the time, allowing for planning to prevent repeated bleeding (e.g., clipping or coiling of the responsible aneurysm). »**EEG:** decreased voltage or variability of alpha frequency Can be useful in showing the first signs of vasospasm.

Encephalitis

History	Exam	1st Test	Other tests
initial fever and malaise followed by speech difficulty, seizures, behavioral changes, impaired alertness; history of overseas travel; history of recent infection with infectious mononucleosis, measles, or rubella; may also experience convulsions	cognitive testing demonstrates language disturbance (aphasia, paraphasic errors in speech, anomia, apraxia) and evidence of temporal lobe seizures (staring, unresponsiveness, automatisms); West Nile encephalitis: may have bulbar paralysis and quadriplegia	»**MRI brain:** hyperintensities in the medial temporal lobe and insular cortex on 1 or both sides Given a compatible clinical picture this is almost diagnostic of herpes simplex encephalitis. Consider limbic encephalitis (an autoimmune disorder that is often a paraneoplastic syndrome) if only medial temporal lobe structures are involved.	»**CBC:** WBC count reduced, normal, or elevated »**CSF analysis:** polymerase chain reaction (PCR) positive for causative virus; usually lymphocytic pleocytosis with elevated protein and normal glucose Prior neuroimaging is wise to exclude significant mass effect, which can make lumbar puncture hazardous. PCR is highly specific and sensitive and is positive in 90% of

Uncommon

Encephalitis

History	Exam	1st Test	Other tests
			cases. Diagnosis can be confirmed by finding IgM antibodies for certain viruses (herpes simplex virus, rabies virus, arthropod-borne virus) in the CSF. »**EEG:** periodic lateralized epileptiform discharges (PLEDs) over 1 or both temporal lobes PLEDs can be seen in other acute/subacute structural lesions but, given context, are sensitive in >80% of cases of acute herpes simplex encephalitis; can be helpful in monitoring for seizures.

Brain abscess

History	Exam	1st Test	Other tests
progressively worsening headache, seizures; mass effect/ herniation: usually progressive impairment of consciousness, one-sided weakness, visual disturbance, hearing disturbance, taste disturbance, difficulty swallowing, facial paralysis, and/or difficulty breathing	body temperature may not be elevated, progression of focal signs; mass effect/ herniation: usually progressive impairment of consciousness, hemiparesis, oculomotor palsy, cranial nerve palsies, respiratory arrest, hypertension, hypotension, and/or brain death	»**CT head:** intra- or extracerebral mass effect with displacement of midline structures (septum pellucidum or pineal by >9 mm from the midline); rim of enhancement around the abscess is typically thin and uniform, as opposed to malignant glial tumors, which typically have walls of variable thickness CT is usually more readily available and faster than MRI, but it	»**CBC:** normal or elevated WBC count with left shift WBC count is not reliably elevated. »**MRI brain:** abscess and surrounding edema; shows earlier smaller abscess if >1 is present (e.g., in bacterial endocarditis) Usually performed later. MRI can provide more detail than CT.

Uncommon

Brain abscess

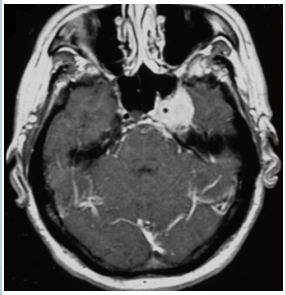
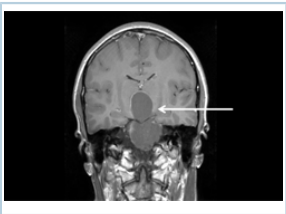
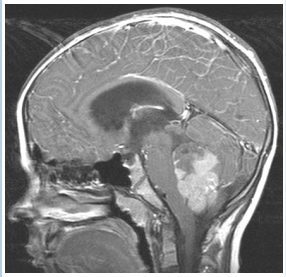
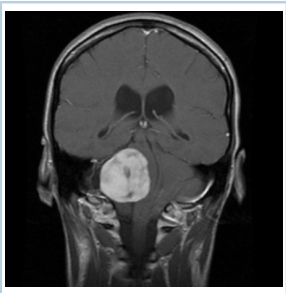
History	Exam	1st Test	Other tests
		may provide less detail. Unenhanced scans are performed first and then contrast is added if needed to clarify nature of mass (e.g., differentiation of tumor from brain abscess). »**blood culture:** normal or positive with bacterial or fungal sepsis Important to do, although results are often negative.	

Brain tumor

History	Exam	1st Test	Other tests
often progressive headache; eloquent area tumor: weakness, reduced sensation, speech problems; frontal lobe tumor: seizures; mass effect/ herniation: usually progressive impairment of consciousness, one-sided weakness, visual disturbance, hearing disturbance, taste disturbance, difficulty swallowing, facial paralysis, and/or difficulty breathing	eloquent area tumor: lateralized weakness, sensory changes, dysphasia; mass effect/ herniation: usually progressive impairment of consciousness, hemiparesis, oculomotor palsy, cranial nerve palsies, respiratory arrest, hypertension, hypotension, and/or brain death	»**CT head:** intra- or extracerebral mass effect with displacement of midline structures (septum pellucidum or pineal by >9 mm from the midline) CT is usually more readily available and faster than MRI, but it may provide less detail. Unenhanced scans are performed first and then contrast is added if needed to clarify nature of mass (e.g., differentiation of tumor from brain abscess).	»**MRI brain:** intra- or extracerebral mass effect with displacement of midline structures (septum pellucidum or pineal by >9 mm from the midline) Usually performed later. MRI can provide more detail than CT. Can be helpful in showing multiple lesions: for example, metastases.

Uncommon

Brain tumor

History	Exam	1st Test	Other tests
		 *Meningioma: coronal contrast-enhanced image demonstrates meningioma in the cavernous sinus on the left side* From the personal collection of William T. Couldwell; used with permission  *Craniopharyngioma: coronal postcontrast MRI* From the personal collection of Marc C. Chamberlain; used with permission	 *Medulloblastoma: sagittal view MRI showing an avidly enhancing solid and cystic lesion filling the fourth ventricle; obstructive hydrocephalus present* From the collection of Peter B. Storm; used with permission  *Acoustic neuroma: coronal postcontrast MRI* From the collection of Ryojo Akagami; used with permission

Uncommon

Hypernatremia

History	Exam	1st Test	Other tests
thirst, confusion, fever, convulsions, diarrhea, vomiting, burns	clinical dehydration, oliguria	»**serum electrolyte panel:** sodium elevated >145 mmol/L (145 mEq/L) Patients are usually asymptomatic until serum sodium is >160 mmol/L (160 mEq/L). »**ABG:** metabolic acidosis Caused by diarrhea/ vomiting.	»**CT head:** normal »**MRI brain:** normal

◊ Hypercalcemia

History	Exam	1st Test	Other tests
mental slowing and impairment, personality changes, confusion; history of abdominal pain, or kidney stones	encephalopathic features with intact brainstem functioning	»**serum electrolyte panel:** calcium elevated, usually >3 mmol/L or 12 mg/dL Severe CNS dysfunction occurs at >4 mmol/L or 16 mg/dL.	»**serum parathyroid hormone (PTH):** low, normal, or elevated Performed shortly after establishing hypercalcemia. The diagnosis of primary hyperparathyroidism is based on substantial elevation of PTH despite hypercalcemia. The normal range is up to 65 picograms/mL. Multiple myeloma or leukemia may cause slightly low PTH. »**24-hour calcium:** normal or elevated Performed shortly after establishing hypercalcemia. Elevated >400 mg/24 hour with primary hyperparathyroidism.

Uncommon

◊ Hypercalcemia

History	Exam	1st Test	Other tests
			»**skeletal survey:** normal, osteopenia, osteolytic lesions, pathologic fractures Performed shortly after establishing hypercalcemia. If positive, may indicate multiple myeloma, leukemia, or bone secondaries. »**CT head:** normal

Hypocalcemia

History	Exam	1st Test	Other tests
behavioral changes, abdominal pain, fatigue, muscle weakness, cramps, fractures, seizures	papilledema, raised intracranial pressure; occasionally, hyperreflexia, positive Chvostek and Trousseau signs, tetany, laryngeal stridor	»**serum electrolyte panel:** reduced calcium It is most helpful to measure serum ionized calcium (usually <0.5 mmol/L) or total serum calcium (<1.8 mmol/L or 7.0 mg/dL). If measuring total serum concentrations, consider serum albumin, as calcium is albumin-bound (corrected [Ca] = measured [Ca] + [40-{albumin} x 0.02 for g or mg/L]).	»**CT head:** normal

Hypermagnesemia

History	Exam	1st Test	Other tests
preceding/coincident renal failure; weakness	areflexia; occasionally pupils dilated and fixed	»**serum electrolyte panel:** elevated Mg	»**CT head:** normal

Uncommon

Hypermagnesemia

History	Exam	1st Test	Other tests
		Clinical features are usually only present when serum Mg is >2-3.5 mmol/L (5-8 mg/dL). »**ABG:** normal or hypercapnia, indicating respiratory failure Hypercapnia, indicating respiratory failure is one of the main life-threatening complications of hypermagnesemia. Patients may require intubation and assisted ventilation in the intensive care unit (ICU).	

◊ Hypomagnesemia

History	Exam	1st Test	Other tests
seizures	dysphagia, athetosis, papilledema, raised intracranial pressure; occasionally hemiplegia	»**serum electrolyte panel:** reduced Mg <1.0 mmol/L (<2.0 mEq/L)	»**CT head:** normal

◊ Porphyria

History	Exam	1st Test	Other tests
acute confusion, hallucinations, psychotic behavior, anxiety, depression; abdominal, limb, chest, back pain; weakness; stupor, coma; seizures	peripheral neuropathy; sweating, tachycardia, hypertension, evidence of impairment	»**urinary porphobilinogen (PBG):** elevated, reddish color Elevated concentrations are usually marked during attacks. The presence of PBG	

Uncommon

◊ Porphyria

History	Exam	1st Test	Other tests
		can be confirmed in a single-void urine specimen using a PBG test kit. »**urinary delta-aminolevulinic acid:** elevated	

Mitochondrial disorder

History	Exam	1st Test	Other tests
intermittent stroke-like events, seizures, visual disturbances	short stature, hearing impairment, visual field defects or cortical blindness, ophthalmoplegia, ataxia, cardiomyopathy, polyneuropathy in varied combinations	»**serum lactic acid:** elevated during attacks »**muscle biopsy:** ragged red fibers, stains of succinate dehydrogenase show prominent staining of endothelium	»**ABG:** metabolic acidosis Caused by lactic acidosis. »**mitochondrial genetic testing:** mutations and/or deletions Performed after preliminary investigations to define the clinical syndrome. »**MRI brain:** normal or discrete metabolic strokes Often helpful but may not be sufficiently specific. Can show discrete metabolic strokes that often do not respect arterial territories.

◊ Thyroid storm

History	Exam	1st Test	Other tests
history of hyperthyroidism, fever, profuse sweating,	fever >101.3°F (>38.5°C) initially followed by	»**diagnostic criteria score:** ≥45: highly	»**TSH:** suppressed

Uncommon

◊ Thyroid storm

History	Exam	1st Test	Other tests
weight loss, fatigue, nausea and vomiting, diarrhea, abdominal pain, anxiety, altered behavior, seizures; history of triggering factors, including sepsis, surgery, anesthesia induction, radioactive iodine therapy, use of known causative medications (anticholinergics, adrenergics, nonsteroidal anti-inflammatory drugs [NSAIDs], chemotherapy, excessive thyroxine), withdrawal of or noncompliance with antithyroid medication, trauma to or vigorous palpation of the thyroid, pregancy, labor, DKA	hyperpyrexia, tachycardia disproportionate to fever, goiter, Graves ophthalmopathy, hyperreflexia with transient pyramidal signs, signs of high-output heart failure	suggestive; 25-44: likely; <25: unlikely Score is based on the severity of thermoregulatory dysfunction, GI-hepatic dysfunction, tachycardia, heart failure, CNS effects, and the presence or absence of known triggers.[100] »**ECG:** may show supraventricular or ventricular tachycardia	Only useful if the patient is not already known to have hyperthyroidism. »**serum free T4:** elevated Only useful if the patient is not already known to have hyperthyroidism.

Burns

History	Exam	1st Test	Other tests
pain; may be evidence of abuse or neglect in children	airway edema; clouded cornea; erythema, cellulitis	»**none:** diagnosis is usually apparent on clinical evaluation	»**EEG:** mild: slowing pattern; severe: burst-suppression pattern EEGs show a graded pattern of severity. Mortality is 70% with the burst suppression patterns, but patients die of multiorgan failure rather than nervous system complications.

Uncommon

◊ Hyperthermia

History	Exam	1st Test	Other tests
history of heat stroke, hot environment, stroke, trauma, encephalitis, sepsis, cocaine or amphetamine abuse; seizures	core body temperature >101.3°F (38.5°C); >107.6°F (42°C) causes coma	»**CBC:** elevated WBC count if sepsis »**blood culture:** normal or positive	»**EEG:** slowing pattern Hyperthermia often causes seizures.

Hypothermia

History	Exam	1st Test	Other tests
coma preceded by delirium and then stupor as temperature drops; may be accidental; may be a history of hypothalamic disorder, spinal cord injury, hypothyroidism, adrenal failure, Wernicke encephalopathy, advanced sepsis, sedative drug intoxication	core body temperature <95°F (35°C); <82.4°F (28°C) usually causes coma; pupillary light reflex absent, resembling brain death	»**CBC:** normal or elevated WBC count WBC count can be elevated in cases of sepsis (sometimes associated with low body temperature in older or disabled patients). »**blood culture:** normal or positive Worth doing to help rule out infection, especially in older patients. »**thyroid function tests:** reduced triiodothyronine/ thyroxine if hypothyroidism Hypothyroidism may cause hypothermia. »**ECG:** Ventricular fibrillation, cardiac arrest At core temperatures <82.4°F (28°C), there is a risk of ventricular fibrillation and cardiac arrest.	»**EEG:** wave patterns vary with core temperature: <86°F (30°C): evolutionary changes with slowing pattern; <71.6°F (20°C to 22°C): changes to burst-suppression pattern; <68°F (20°C): isoelectric pattern These changes are thought to reflect a progressive failure of synaptic transmission in the brain.

Uncommon

◊ Psychogenic unresponsiveness

History	Exam	1st Test	Other tests
usually female, odd behavior, weeping, verbalizing, psychosocial problems, abuse, nonepileptic pseudoseizures, psychogenic seizures; uncommon in childhood or age >60 years	nystagmus with caloric testing implies patient conscious; variety of behavior (e.g., eyes facing floor, rolling over to avoid being tickled, eyes closed during seizure, holding/shaking bed sides, asynchronous movements during seizure), or motionless	»**EEG:** normal awake pattern with alpha rhythm blocking and passive eye opening No seizure activity during the ictus. This test is often not necessary if the episode is captured on video or witnessed, but does add conclusive evidence.	»**ABG:** pseudoseizures: normal or respiratory alkalosis from hyperventilation Readily available and of some confirmatory value. Convulsive seizure shows a profound, mixed metabolic-respiratory acidosis.

Locked-in state

History	Exam	1st Test	Other tests
basis pontis lesions: sudden/stuttering onset, communication with eye movement; central pontine myelinolysis: systemically ill inpatients, history of sudden sodium/ osmolality elevation; polyneuropathy: gradual onset, cranial nerve palsy; pharmacological paralysis: ICU/ postsurgical recovery room onset	consciousness preserved but impaired motor output; basis pontis lesions: upper motor neuron palsy of lower cranial nerves and 4 limbs, vertical eye movement, eyes open and close voluntarily; polyneuropathy: no vertical eye movement, may lose pupillary reflexes, absent deep tendon reflexes; pharmacological paralysis: intact pupillary reflexes	»**MRI brain:** basis pontis lesion: infarct, hemorrhage, or demyelinative lesion in basis pontis »**EMG:** acute inflammatory demyelinative polyneuropathy (AIDP) or Guillain-Barre syndrome: prolonged "f waves"/conduction block The "train of 4" in the ICU transcutaneous nerve stimulation (usually of the median nerve) looks for muscle response. Neuromuscular blockade demonstrated in AIDP and Guillain-Barre syndrome.	»**CSF exam:** elevated protein with no or few WBCs; AIDP: classic albuminocytological dissociation

Online resources

1. The FOUR Score *(external link) (https://www.coma.uliege.be/severe-brain-injury)*

Evidence tables

What are the effects of early versus late initiation of empiric antimicrobial treatment in adults with or at risk of developing sepsis or severe sepsis?[56]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.nice.org.uk/guidance/ng51/evidence)

Evidence C *	Confidence in the evidence is very low or low where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Adults with or at risk of developing sepsis or severe sepsis
Intervention: Early initiation of empiric antimicrobial treatment
Comparison: Late initiation of empiric antimicrobial treatment

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
<1 hour versus >1 hour		
Mortality [a]	Favors intervention	Very Low
Mortality - Intensive Care Unit (ICU) setting	Favors intervention	Very Low
Mortality - Emergency Department (ED) setting	No statistically significant difference	Very Low
<2 hours versus >2 hours		
Mortality [a]	No statistically significant difference	Very Low
Mortality - ICU setting	Favors intervention	Very Low
Mortality - ED setting	No statistically significant difference	Very Low
<3 hours versus >3 hours		
Mortality [a]	Favors intervention	Very Low
Mortality - ICU setting	No statistically significant difference	Very Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Mortality - ED setting	Favors intervention	Very Low
<4 hours versus >4 hours		
Mortality - ED setting	No statistically significant difference	Very Low
<5 hours versus >5 hours		
Mortality - ED setting	No statistically significant difference	Very Low
<6 hours versus >6 hours		
Mortality [a]	Favors intervention	Very Low
Mortality - ICU setting	No statistically significant difference	Very Low
Mortality - ED setting	Favors intervention	Very Low

Recommendations as stated in the source guideline

The guideline committee recommends that adults, children, and young people over the age of 12 who have suspected sepsis and one or more high-risk criteria, should be given a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour of establishing they meet high-risk criteria in an acute hospital setting).[b] See guideline for details on criteria for different levels of risk.

Note

Results in this table are based on observational studies only.

[a] Includes overall mortality in intensive care and emergency department settings.

[b] This guideline recommends that all people with suspected sepsis have a face-to-face assessment and a risk stratification tool is used to determine risk of severe illness and death from sepsis. Recommendations depend on the presence and number of high-, moderate-to-high, and low-risk criteria.

What are the effects of early versus late initiation of empiric antimicrobial treatment in children with or at risk of developing sepsis or severe sepsis?[56]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.nice.org.uk/guidance/ng51/evidence)

Evidence C *	Confidence in the evidence is very low or low where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Children with or at risk of developing sepsis or severe sepsis
Intervention: Early initiation of empiric antimicrobial treatment
Comparison: Late initiation of empiric antimicrobial treatment

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
<1 hour versus >1 hour [a]		
Pediatric Intensive Care Unit (PICU) mortality	No statistically significant difference	Very Low
<2 hours versus >2 hours [a]		
PICU mortality	No statistically significant difference	Very Low
<3 hours versus >3 hours [a]		
PICU mortality	Favors intervention	Very Low
<4 hours versus >4 hours [a]		
PICU mortality	Favors intervention	Very Low

Recommendations as stated in the source guideline
The National Institute of Health and Care Excellence (NICE) 2016 guideline on Sepsis: recognition, diagnosis and early management makes the following recommendation:

For children aged 5–11 years who have suspected sepsis and 1 or more high-risk criteria, give a broad-spectrum antimicrobial [b] at the maximum recommended dose without delay (within 1 hour of identifying that they meet any high-risk criteria in an acute hospital setting).

Note
The guideline group noted that the direct evidence in children came from one small (n=130), single-centre retrospective study of children in PICU with severe sepsis and septic shock. Therefore, they also

extrapolated from the indirect evidence in adults to make the same recommendation for all age groups (including children aged under 5 years and 5-11 years).

[a] Time from sepsis recognition to initial treatment and first appropriate treatment.

[b] See full guideline for more information.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- Greer DM, Kirschen MP, Lewis A, et al. Pediatric and adult brain death/death by neurologic criteria consensus guideline. Neurology. 2023 Dec 12;101(24):1112-32. Full text (https://www.neurology.org/doi/10.1212/WNL.0000000000207740) Abstract
- National Institute for Health and Care Excellence. Head injury: assessment and early management. Sep 2023 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng232)
- Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury 4th edition. September 2016 [internet publication]. Full text (https://braintrauma.org/coma/guidelines/guidelines-for-the-management-of-severe-tbi-4th-ed)

References

1. Posner JB, Saper CB, Schiff ND, et al. Psychogenic unresponsiveness. Plum and Posner's diagnosis of stupor and coma. New York, NY: Oxford University Press; 2007.
2. Wijdicks EFM. The comatose patient. New York, NY: Oxford University Press; 2007.
3. Young GB, Wijdicks EFM, eds. Disorders of consciousness. Volume 90. The Handbook of Clinical Neurology, 3rd series. New York, NY: Elsevier; 2008.
4. Sporns O. Structure and function of complex brain networks. Dialogues Clin Neurosci. 2013 Sep;15(3):247-62. Full text (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3811098) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24174898?tool=bestpractice.bmj.com)
5. Bodien YG, Carlowicz CA, Chatelle C, et al. Sensitivity and specificity of the coma recovery scale--revised total score in detection of conscious awareness. Arch Phys Med Rehabil. 2016 Mar;97(3):490-492.e1. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26342571?tool=bestpractice.bmj.com)
6. Greer DM, Kirschen MP, Lewis A, et al. Pediatric and adult brain death/death by neurologic criteria consensus guideline. Neurology. 2023 Dec 12;101(24):1112-32. Full text (https://www.neurology.org/doi/10.1212/WNL.0000000000207740) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37821233?tool=bestpractice.bmj.com)
7. Laureys S, Celesia GG, Cohadon F, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010 Nov 1;8:68. Full text (https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-8-68) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21040571?tool=bestpractice.bmj.com)
8. Vincent SR. The ascending reticular activating system - from aminergic neurons to nitric oxide. J Chem Neuroanat. 2000 Feb;18(1-2):23-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10708916?tool=bestpractice.bmj.com)

9. Department of Health. Hospital Episode Statistics (England). 2002-2003 [internet publication]. Full text (http://www.hscic.gov.uk/hes)

10. Matthes G, Bernhard M, Kanz KG, et al. Emergency anesthesia, airway management and ventilation in major trauma. Background and key messages of the interdisciplinary S3 guidelines for major trauma patients [in German]. Unfallchirurg. 2012 Mar;115(3):251-64. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22406918?tool=bestpractice.bmj.com)

11. Bruno MA, Ledoux D, Lambermont B, et al. Comparison of the Full Outline of UnResponsiveness and Glasgow Liege Scale/Glasgow Coma Scale in an intensive care unit population. Neurocrit Care. 2011 Dec;15(3):447-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21526394?tool=bestpractice.bmj.com)

12. Meschia JF, Bushnell C, Boden-Albala B, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Dec;45(12):3754-832. Full text (http://stroke.ahajournals.org/content/45/12/3754.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25355838?tool=bestpractice.bmj.com)

13. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke. 2021 Jul;52(7):e364-467. Full text (https://www.ahajournals.org/doi/10.1161/STR.0000000000000375) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34024117?tool=bestpractice.bmj.com)

14. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke. 2022 Jul;53(7):e282-361. Full text (https://www.ahajournals.org/doi/10.1161/STR.0000000000000407) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35579034?tool=bestpractice.bmj.com)

15. Hoh BL, Ko NU, Amin-Hanjani S, et al. 2023 guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke. 2023 Jul;54(7):e314-70. Full text (https://www.doi.org/10.1161/STR.0000000000000436) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37212182?tool=bestpractice.bmj.com)

16. Centers for Disease Control and Prevention. Traumatic brain injury & concussion: prevention. May 2021 [internet publication]. Full text (https://www.cdc.gov/traumaticbraininjury/prevention.html)

17. National Institute for Health and Care Excellence. Head injury: assessment and early management. Sep 2023 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng232)

18. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury 4th edition. September 2016 [internet publication]. Full text (https://braintrauma.org/coma/guidelines/guidelines-for-the-management-of-severe-tbi-4th-ed)

19. Pandor A, Harnan S, Goodacre S, et al. Diagnostic accuracy of clinical characteristics for identifying CT abnormality after minor brain injury: a systematic review and meta-analysis. J Neurotrauma. 2012 Mar 20;29(5):707-18. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21806474?tool=bestpractice.bmj.com)

20. Coffeng SM, Foks KA, van den Brand CL, et al. Evaluation of clinical characteristics and CT decision rules in elderly patients with minor head injury: a prospective multicenter cohort study. J Clin Med. 2023 Jan 27;12(3). Full text (https://www.mdpi.com/2077-0383/12/3/982) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36769631?tool=bestpractice.bmj.com)

21. Kim YJ. A systematic review of factors contributing to outcomes in patients with traumatic brain injury. J Clin Nurs. 2011 Jun;20(11-12):1518-32. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21453293?tool=bestpractice.bmj.com)

22. Oliveira L, Fregni F. Pharmacological and electrical stimulation in chronic disorders of consciousness: new insights and future directions. Brain Inj. 2011;25(4):315-27. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21314279?tool=bestpractice.bmj.com)

23. Cowperthwaite MC, Burnett MG. The association between weather and spontaneous subarachnoid hemorrhage: an analysis of 155 US hospitals. Neurosurgery. 2011 Jan;68(1):132-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21099710?tool=bestpractice.bmj.com)

24. Wilson JX, Young GB. Sepsis-associated encephalopathy: evolving concepts. Can J Neurol Sci. 2003 May;30(2):98-105. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12774948?tool=bestpractice.bmj.com)

25. Huang Y, Chen R, Jiang L, et al. Basic research and clinical progress of sepsis-associated encephalopathy. J Intensive Med. 2021 Oct;1(2):90-5. Full text (https://www.sciencedirect.com/science/article/pii/S2667100X21000293?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36788800?tool=bestpractice.bmj.com)

26. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008 Dec;7(12):1091-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18851928?tool=bestpractice.bmj.com)

27. Graus F, Saiz A, Lai M, et al. Neuronal surface antigen antibodies in limbic encephalitis: clinical-immunologic associations. Neurology. 2008 Sep 16;71(12):930-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18794496?tool=bestpractice.bmj.com)

28. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009 Apr;65(4):424-34. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19338055?tool=bestpractice.bmj.com)

29. Hjalmarsson A, Blomqvist P, Sköldenberg B. Herpes simplex encephalitis in Sweden, 1990-2001: incidence, morbidity, and mortality. Clin Infect Dis. 2007 Oct 1;45(7):875-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17806053?tool=bestpractice.bmj.com)

30. Ropper AH, Gorson KC. Clinical practice: concussion. N Eng J Med. 2007 Jan 11;356(2):166-72. Full text (http://www.nejm.org/doi/full/10.1056/NEJMcp064645) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17215534?tool=bestpractice.bmj.com)

31. Shaw NA. The neurophysiology of concussion. Prog Neurobiol. 2002 Jul;67(4):281-344. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12207973?tool=bestpractice.bmj.com)

32. Holbourn AH. The mechanics of brain injuries. Br Med Bull. 1945;3:147-9.

33. Povlishock JT, Christman CW. The pathobiology of traumatically induced axonal injury in animals and humans. J Neurotrauma. 1995 Aug;12(4):555-64. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8683606?tool=bestpractice.bmj.com)

34. Moulton R. Head Injury. In: Young GB, Ropper AH, Bolton CF, eds. Coma and impaired consciousness: a clinical perspective. New York, NY: McGraw-Hill; 1998:149-181.

35. Young GB, Doig GS. Continuous EEG monitoring in comatose intensive care unit patients: epileptiform activity in etiologically distinct groups. Neurocrit Care. 2005;2(1):5-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16174961?tool=bestpractice.bmj.com)

36. Calland JF, Ingraham AM, Martin N, et al. Evaluation and management of geriatric trauma: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012 Nov;73(5 Suppl 4):S345-50. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23114492?tool=bestpractice.bmj.com)

37. Grubb BP. Clinical practice: neurocardiac syncope. N Engl J Med. 2005 Mar 10;352(10):1004-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15758011?tool=bestpractice.bmj.com)

38. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000 Feb 28;160(4):526-34. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10695693?tool=bestpractice.bmj.com)

39. Gajdos PH, Korach JM, Conso F, et al. Epidemiological investigation of acute carbon monoxide poisoning (A-CMP) in the Hauts-de-Seine department. Intensive Care Med. 1988;14:434-40.

40. Friedman Y, Lee L, Wherrett JR, et al. Simulation of brain death from fulminant de-efferentation. Can J Neurol Sci. 2003 Nov;30(4):397-404. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14672276?tool=bestpractice.bmj.com)

41. Benbadis SR, Agrawal V, Tatum WO. How many patients with psychogenic nonepileptic seizures also have epilepsy? Neurology. 2001 Sep 11;57(5):915-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11552032?tool=bestpractice.bmj.com)

42. Lindboe CF, Loberg EM. Wernicke's encephalopathy in nonalcoholics: an autopsy study. J Neurol Sci. 1989 Apr;90(2):125-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2723677?tool=bestpractice.bmj.com)

43. Koguchi K, Nakatsui Y, Abe K, et al. Wernicke's encephalopathy after glucose infusion. Neurology. 2004 Feb 10;62(3):512. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14872047?tool=bestpractice.bmj.com)

44. Dunn LT, Fitzpatrick MO, Beard D, et al. Patients with a head injury who "talk and die" in the 1990s. J Trauma. 2003 Mar;54(3):497-502. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12634529?tool=bestpractice.bmj.com)

45. Schmahmann JD. Vascular syndromes of the thalamus. Stroke. 2003 Sep;34(9):2264-78. Full text (http://stroke.ahajournals.org/cgi/content/full/34/9/2264) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12933968?tool=bestpractice.bmj.com)

46. Fujioka M, Okuchi K, Hiramatsu KI, et al. Specific changes in the human brain after hypoglycemic injury. Stroke. 1997 Mar;28(3):584-7. Full text (http://stroke.ahajournals.org/cgi/content/full/28/3/584) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9056615?tool=bestpractice.bmj.com)

47. Abraham MB, Karges B, Dovc K, et al. ISPAD clinical practice consensus guidelines 2022: assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2022 Dec;23(8):1322-40. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10107518)

48. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2021 Dec;64(12):2609-52. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8481000) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34590174?tool=bestpractice.bmj.com)

49. National Institute for Health and Care Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. May 2023 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng18)

50. ElSayed NA, Aleppo G, Aroda VR, et al. 6. Glycemic targets: standards of care in diabetes-2023. Diabetes Care. 2023 Jan 1;46(suppl 1):S97-110. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9810469) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36507646?tool=bestpractice.bmj.com)

51. Desimone ME, Weinstock RS. Hypoglycemia. South Dartmouth (MA): MDText.com, Inc; 2000.

52. Masuhr F, Mehraien S, Einhaupl K. Cerebral venous and sinus thrombosis. J Neurol. 2004 Jan;251(1):11-23. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14999484?tool=bestpractice.bmj.com)

53. Ulivi L, Squitieri M, Cohen H, et al. Cerebral venous thrombosis: a practical guide. Pract Neurol. 2020 Oct;20(5):356-67. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32958591?tool=bestpractice.bmj.com)

54. Roos KL. Infectious etiologies of altered consciousness. Hand Clin Neurol. 2008;90:201-16. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18631824?tool=bestpractice.bmj.com)

55. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10. Full text (https://jamanetwork.com/journals/jama/fullarticle/2492881) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26903338?tool=bestpractice.bmj.com)

56. National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management. Mar 2024 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng51)

57. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-143. Full text (https://journals.lww.com/ccmjournal/fulltext/2021/11000/surviving_sepsis_campaign__international.21.aspx)

58. Royal College of Physicians. National Early Warning Score (NEWS) 2. Dec 2017 [internet publication]. Full text (https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2)

59. American College of Emergency Physicians (ACEP) Expert Panel on Sepsis. DART: an evidence-driven tool to guide the early recognition and treatment of sepsis and septic shock [internet publication]. Full text (https://poctools.acep.org/POCTool/Sepsis(DART)/276ed0a9-f24d-45f1-8d0c-e908a2758e5a)

60. Academy of Medical Royal Colleges. Statement on the initial antimicrobial treatment of sepsis. Oct 2022 [internet publication]. Full text (https://www.aomrc.org.uk/wp-ontent/uploads/2022/10/Statement_on_the_initial_antimicrobial_treatment_of_sepsis_V2_1022.pdf)

61. Schlapbach LJ, Watson RS, Sorce LR, et al. International consensus criteria for pediatric sepsis and septic shock. JAMA. 2024 Feb 27;331(8):665-74. Full text (https://jamanetwork.com/journals/jama/fullarticle/2814297) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38245889?tool=bestpractice.bmj.com)

62. Society of Critical Care Medicine. Surviving Sepsis Campaign Hour-1 bundle. 2019 [internet publication]. Full text (https://www.sccm.org/SurvivingSepsisCampaign/Guidelines)

63. Vannatta JB, Whang R, Papper S. Efficacy of intravenous phosphorus therapy in the severely hypophosphatemic patient. Arch Intern Med. 1981 Jun;141(7):885-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7235807?tool=bestpractice.bmj.com)

64. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Eng J Med. 1996 Feb 22;334(8):494-500. Full text (http://www.nejm.org/doi/full/10.1056/NEJM199602223340803#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8559202?tool=bestpractice.bmj.com)

65. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med. 2000 Jan 6;342(1):29-36. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10620647?tool=bestpractice.bmj.com)

66. Elder PT. Accidental hypothermia. In: Shoemaker W, ed. Textbook of critical care. Philadelphia, PA: WB Saunders; 1989:101-109.

67. Arrich J, Schütz N, Oppenauer J, et al. Hypothermia for neuroprotection in adults after cardiac arrest. Cochrane Database Syst Rev. 2023 May 22;5(5):CD004128. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004128.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37217440?tool=bestpractice.bmj.com)

68. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: reducing brain injury following cardiopulmonary resuscitation: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2017 May 30;88(22):2141-49. Full text (http://n.neurology.org/content/88/22/2141.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28490655?tool=bestpractice.bmj.com)

69. Amacher SA, Blatter R, Briel M, et al. Predicting neurological outcome in adult patients with cardiac arrest: systematic review and meta-analysis of prediction model performance. Crit Care. 2022 Dec 11;26(1):382. Full text (https://ccforum.biomedcentral.com/articles/10.1186/s13054-022-04263-y) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36503620?tool=bestpractice.bmj.com)

70. Zwingmann J, Mehlhorn AT, Hammer T, et al. Survival and neurologic outcome after traumatic out-of-hospital cardiopulmonary arrest in a pediatric and adult population: a systematic review. Crit Care. 2012 Jul 6;16(4):R117. Full text (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3580693) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22770439?tool=bestpractice.bmj.com)

71. Friberg H, Rundgren M, Westhall E, et al. Continuous evaluation of neurological prognosis after cardiac arrest. Acta Anaesthesiol Scand. 2013 Jan;57(1):6-15. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22834632?tool=bestpractice.bmj.com)

72. Liao KH, Chang CK, Chang HC, et al. Clinical practice guidelines in severe traumatic brain injury in Taiwan. Surg Neurol. 2009 Dec;72 Suppl 2:S66-73. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19818476?tool=bestpractice.bmj.com)

73. Brain Trauma Foundation. Guidelines for the field management of combat-related head trauma. Assessment: Glasgow Coma Scale scoring and assessment of pupils [internet publication].

74. Knuth T, Letarte PB, Ling G, et al; Brain Trauma Foundation. Guidelines for the field management of combat-related head trauma. 2005 [internet publication].

75. Lang CJ, Heidenreich SP, Fahlbusch R, et al. Primary loss of consciousness and amnesia in subarachnoid hemorrhage: a quantitative study [in German]. Zentralbl Neurochir. 2004;65(1):18-24. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14981572?tool=bestpractice.bmj.com)

76. Ahmadi S, Sarveazad A, Babahajian A, et al. Comparison of Glasgow Coma Scale and Full Outline of UnResponsiveness score for prediction of in-hospital mortality in traumatic brain injury patients: a systematic review and meta-analysis. Eur J Trauma Emerg Surg. 2022 Sep 24. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36152069?tool=bestpractice.bmj.com)

77. Almojuela A, Hasen M, Zeiler FA. The Full Outline of UnResponsiveness (FOUR) Score and its use in outcome prediction: a scoping systematic review of the adult literature. Neurocrit Care. 2019 Aug;31(1):162-75. Full text (https://link.springer.com/article/10.1007/s12028-018-0630-9) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30411302?tool=bestpractice.bmj.com)

78. Anestis DM, Tsitsopoulos PP, Tsonidis CA, et al. The current significance of the FOUR score: a systematic review and critical analysis of the literature. J Neurol Sci. 2020 Feb 15;409:116600. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31811988?tool=bestpractice.bmj.com)

79. Vanhaudenhuyse A, Schnakers C, Boly M, et al. Behavioural assessment and functional neuro-imaging in vegetative state patients. Rev Med Liege. 2007;62 Spec No:15-20. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18214355?tool=bestpractice.bmj.com)

80. Morrow SA, Young GB. Selective abolition of the vestibular-ocular reflex by sedative drugs. Neurocrit Care. 2007;6(1):45-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17356191?tool=bestpractice.bmj.com)

81. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005 Dec;20(6):625-33. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16306300?tool=bestpractice.bmj.com)

82. Freund B, Kaplan PW. Post-hypoxic myoclonus: differentiating benign and malignant etiologies in diagnosis and prognosis. Clin Neurophysiol Pract. 2017;2:98-102. Full text (https://www.sciencedirect.com/science/article/pii/S2467981X17300100?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30214979?tool=bestpractice.bmj.com)

83. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology. 1996 Jul;47(1):83-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8710130?tool=bestpractice.bmj.com)

84. American College of Radiology. ACR appropriateness criteria: altered mental status, coma, delirium, and psychosis. 2024 [internet publication]. Full text (https://acsearch.acr.org/docs/3102409/Narrative)

85. Expert Panel on Neurological Imaging, Shih RY, Burns J, et al. ACR appropriateness criteria® head trauma: 2021 Update. J Am Coll Radiol. 2021 May;18(5s):S13-36. Full text (https://www.jacr.org/article/S1546-1440(21)00025-9/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33958108?tool=bestpractice.bmj.com)

86. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Mild Traumatic Brain Injury, Valente JH, Anderson JD, et al. Clinical policy: critical issues in the management of adult patients presenting to the emergency department with mild traumatic brain injury: approved by ACEP board of directors, February 1, 2023 clinical policy endorsed by the Emergency Nurses Association (April 5, 2023). Ann Emerg Med. 2023 May;81(5):e63-105. Full text (https://www.annemergmed.com/article/S0196-0644(23)00028-8/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37085214?tool=bestpractice.bmj.com)

87. Vos PE, Alekseenko Y, Battistin L, et al. Mild traumatic brain injury. Eur J Neurol. 2012 Feb;19(2):191-8. Full text (https://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2011.03581.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22260187?tool=bestpractice.bmj.com)

88. Delorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent non-convulsive status epilepticus following the control of convulsive status epilepticus. Epilepsia. 1998 Aug;39(8):833-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9701373?tool=bestpractice.bmj.com)

89. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000 Jan 25;54(2):340-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10668693?tool=bestpractice.bmj.com)

90. Turi Z, Lenz M, Paulus W, et al. Selecting stimulation intensity in repetitive transcranial magnetic stimulation studies: a systematic review between 1991 and 2020. Eur J Neurosci. 2021 May;53(10):3404-15. Full text (https://onlinelibrary.wiley.com/doi/10.1111/ejn.15195) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33754397?tool=bestpractice.bmj.com)

91. Lescot T, Galanaud D, Puybasset L. Exploring altered consciousness states by magnetic resonance imaging in brain injury. Ann N Y Acad Sci. 2009 Mar;1157:71-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19351357?tool=bestpractice.bmj.com)

92. Wu HM, Huang SC, Hattori N, et al. Selective metabolic reduction in gray matter acutely following human traumatic brain injury. Neurotrauma. 2004 Feb;21(2):149-61. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15000756?tool=bestpractice.bmj.com)

93. Hayashi S, Inaji M, Nariai T, et al. Increased binding potential of brain adenosine A(1) receptor in chronic stages of patients with diffuse axonal injury measured with [1-methyl-(11)C] 8-dicyclopropylmethyl-1-methyl-3-propylxanthine positron emission tomography Imaging. J Neurotrauma. 2018 Jan 1;35(1):25-31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28728462?tool=bestpractice.bmj.com)

94. Lee YC, Phan TG, Jolley DJ, et al. Accuracy of clinical signs, SEP, and EEG in predicting outcome of hypoxic coma: a meta-analysis. Neurology. 2010 Feb 16;74(7):572-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20157159?tool=bestpractice.bmj.com)

95. Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation. Neurology. 2006 Jul 25;67(2):203-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16864809?tool=bestpractice.bmj.com)

96. Carrai R, Grippo A, Lori S, et al. Prognostic value of somatosensory evoked potentials in comatose children: a systematic literature review. Intensive Care Med. 2010 Jul;36(7):1112-26. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20422151?tool=bestpractice.bmj.com)

97. Rajajee V, Muehlschlegel S, Wartenberg KE, et al. Guidelines for neuroprognostication in comatose adult survivors of cardiac arrest. Neurocrit Care. 2023 Jun;38(3):533-63. Full text (https://link.springer.com/article/10.1007/s12028-023-01688-3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36949360?tool=bestpractice.bmj.com)

98. Xu J, Rasmussen IA, Lagopoulos J, et al. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J Neurotrauma. 2007 May;24(5):753-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17518531?tool=bestpractice.bmj.com)

REFERENCES

99. Ashwal S, Babikian T, Gardner-Nicols J, et al. Susceptibility-weighted imaging and proton magnetic resonance spectroscopy in assessment of outcome after pediatric traumatic brain injury. Arch Phys Med Rehabil. 2006 Dec;87(12 Suppl 2):S50-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17140880?tool=bestpractice.bmj.com)

100. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin North Am. 1993 Jun;22(2):263-77. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8325286?tool=bestpractice.bmj.com)

Images

Syndrome	Drug Examples	Features
Sympathomimetic	Cocaine, amphetamines, lysergic acid diethylamide, ephedrine, pseudoephedrine	Increased heart rate and blood pressure; pupils are dilated but reactive, sweating, agitation, hallucinations, seizures
Sympatholytic	Opiates, alpha-2 agonists, sedatives, ethanol	Small but reactive pupils, hypotension, bradycardia, respiratory depression
Cholinergic syndrome	Organophosphates, carbamate insecticides	Increased sweating, small pupils, increased sweating, salivation, bronchial secretions and gastrointestinal activity, confusion, seizures, coma, respiratory failure
Anticholinergic syndrome	First-generation antihistamines, tricyclic antidepressants, benztropine, jimson weed, deadly nightshade	Pupils dilated and often unreactive, tachycardia, decreased sweating, ileus, fever, urinary retention

Figure 1: The principal toxidromes, a constellation of features peculiar to certain classes of drugs

Table created by G. Bryan Young, MD; used with permission

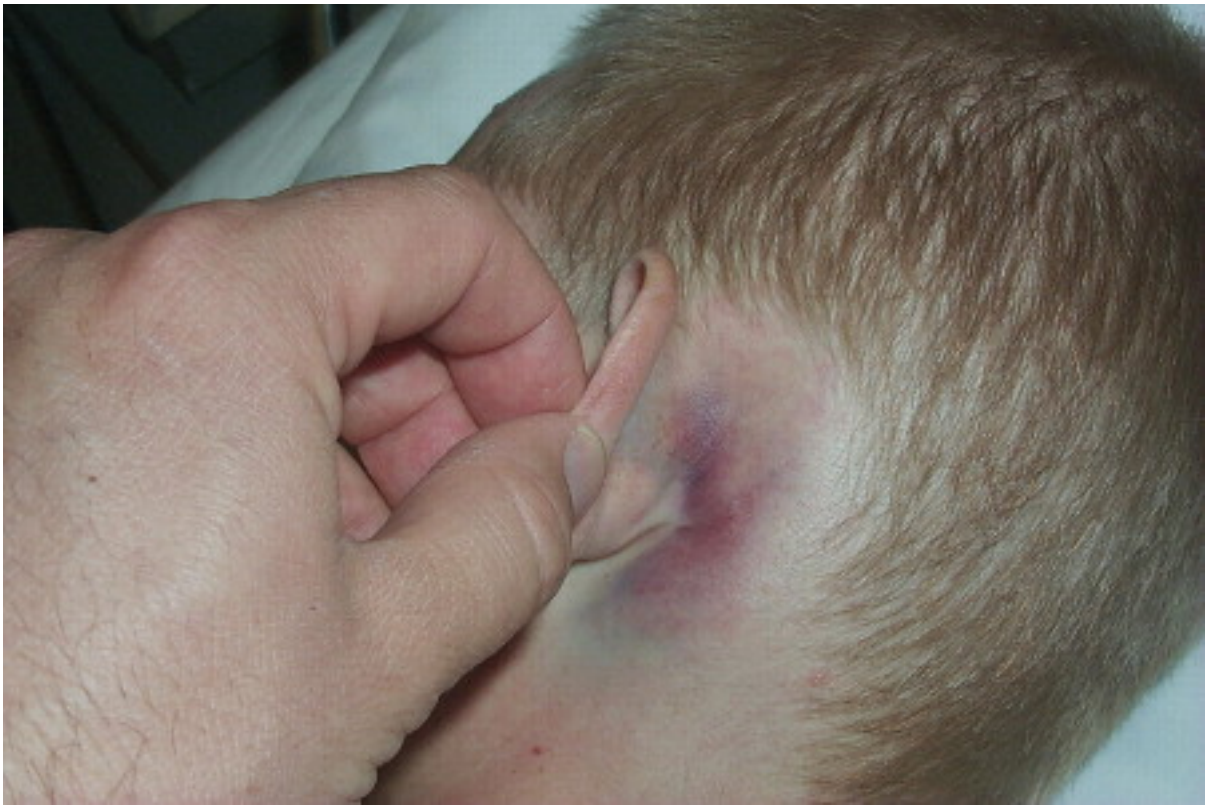


Figure 2: Battle's sign: superficial ecchymosis over the mastoid process

van Dijk GW. Practical Neurology. 2011;11(1):50-55; used with permission

Breathing Pattern	Metabolic Pattern	pH, PaCO2, HCO3	Specific Conditions
Hyperventilation	Metabolic acidosis	pH <7.3, PaCO2 <30 mmHg, HCO3 <17 mmol/L	Uremia, diabetic ketoacidosis, lactic acidosis, salicylates, methanol, ethylene glycol
Hyperventilation	Respiratory Alkalosis	pH>7.45, PaCO2 <30 mmHg, HCO3 >17 mmol/L	Hepatic failure, acute sepsis, acute salicylate intoxication, cardiopulmonary states with hypoxemia, psychogenic causes
Hypoventilation	Respiratory acidosis	pH <7.35 (if acute), PaCO2 > 90 mmHg, HCO3 >17 mmol/L	Respiratory failure from central (e.g., brain or spinal cord) or peripheral nervous system disease, chest conditions or deformities. Coma only with severe hypercarbia.
Hypoventilation	Metabolic alkalosis	pH> 7.45, PaCO2 >45 mm Hg, HCO3 >30 mmol/L	Vomiting, alkali ingestion. Usually no impairment of consciousness; if so, suspect psychogenic unresponsiveness or additional cause.

Figure 3: Respiratory abnormalities, blood gas determination, and diagnostic possibilities

Table created by G. Bryan Young, MD; used with permission

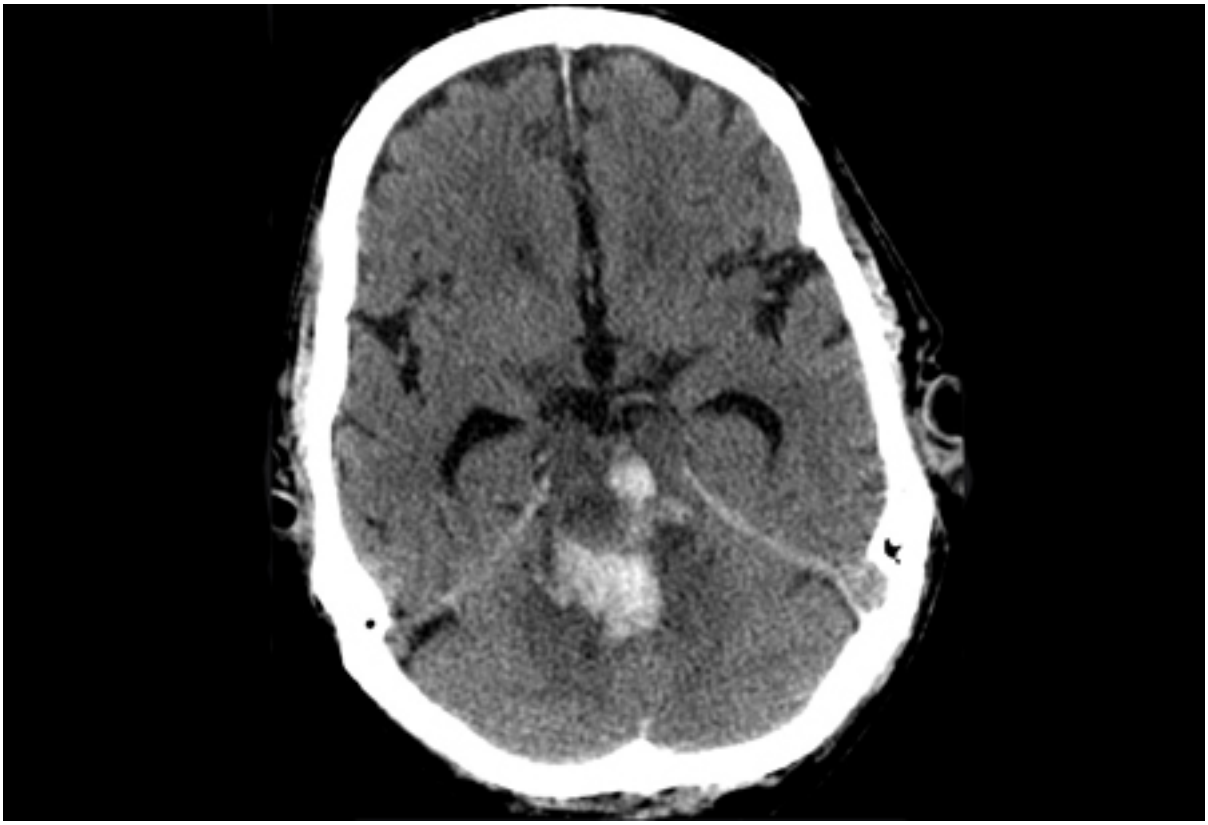


Figure 4: Brainstem hemorrhage in the midbrain that extended from a hypertensive hemorrhage in the pons

From the personal collection of G. Bryan Young, MD; used with permission

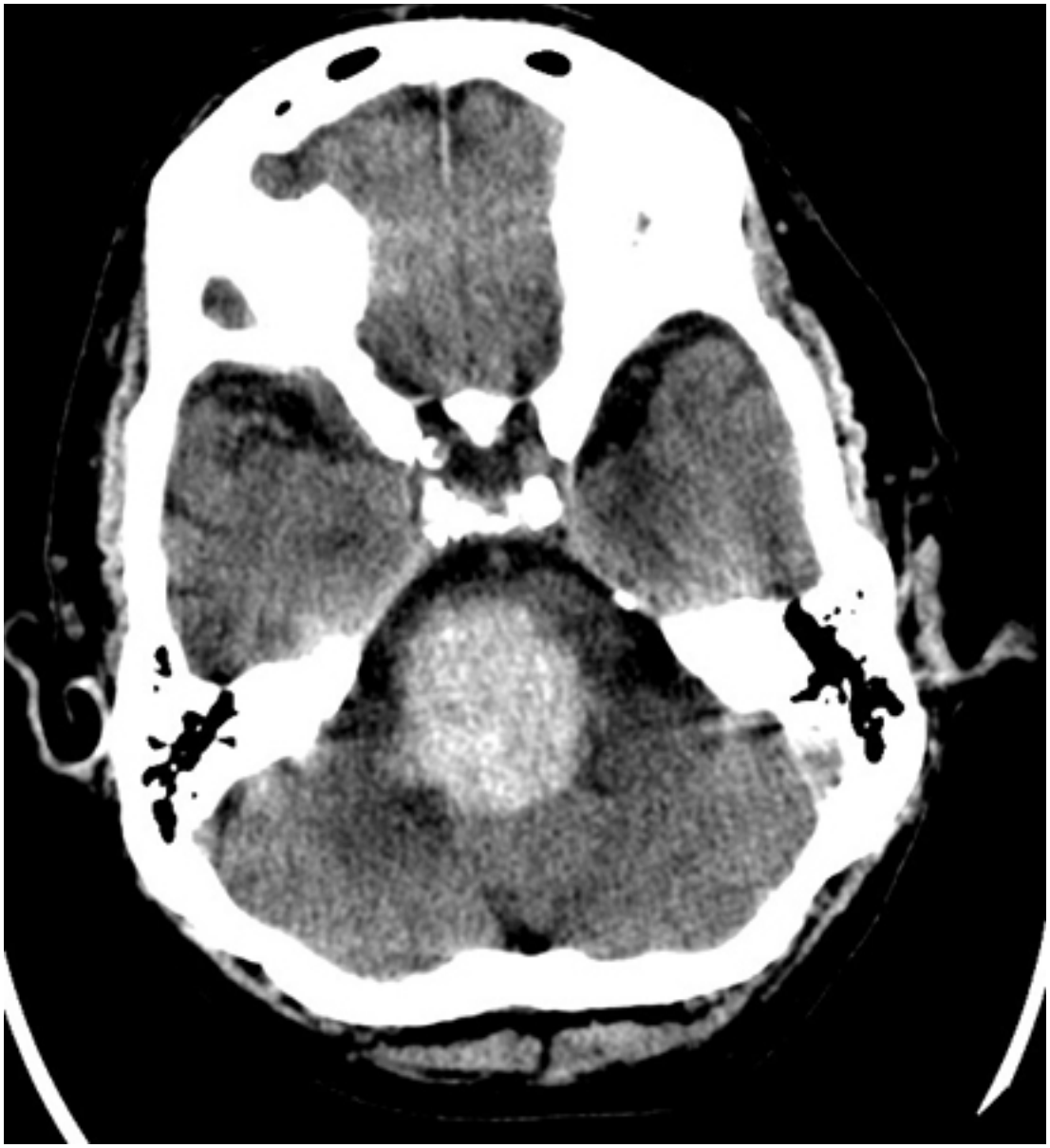


Figure 5: Hypertensive hemorrhage in the pons that ruptured into the fourth ventricle and extended into the midbrain

From the personal collection of G. Bryan Young, MD; used with permission

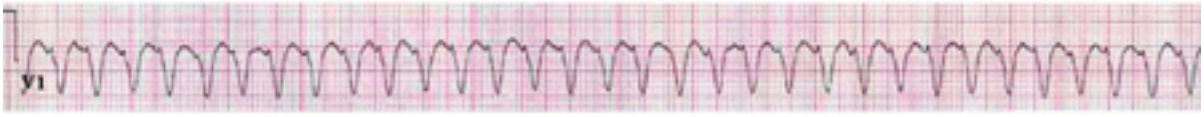


Figure 6: Monomorphic ventricular tachycardia

From the collection of Amar Krishnaswamy; used with permission

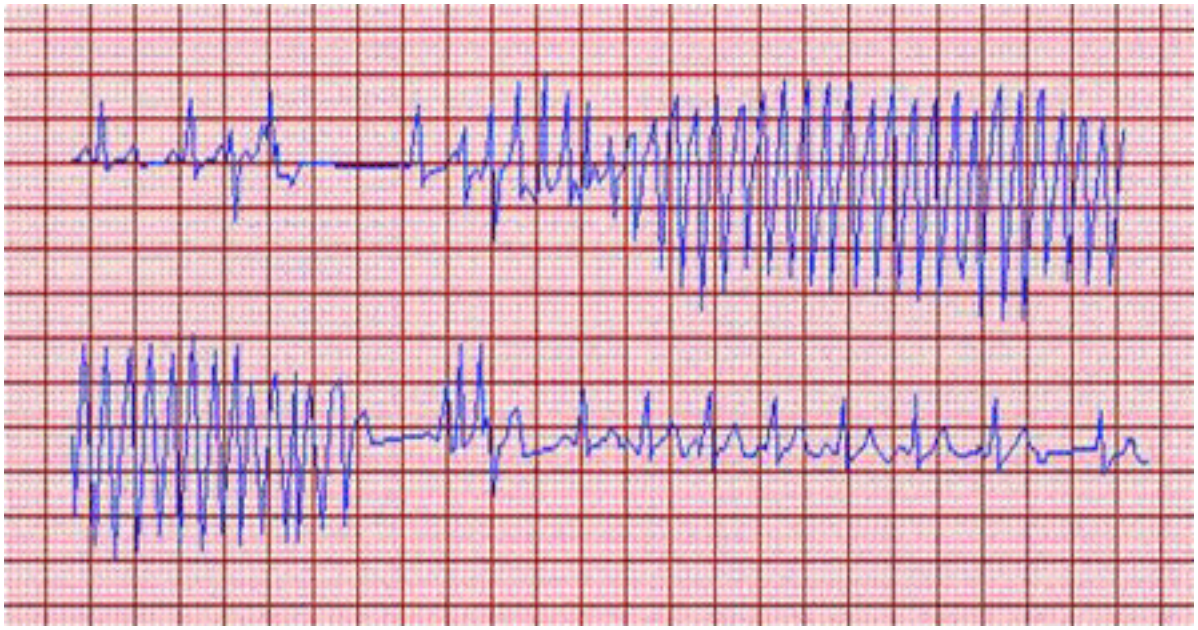


Figure 7: Torsades de pointes

From the collection of Amar Krishnaswamy; used with permission

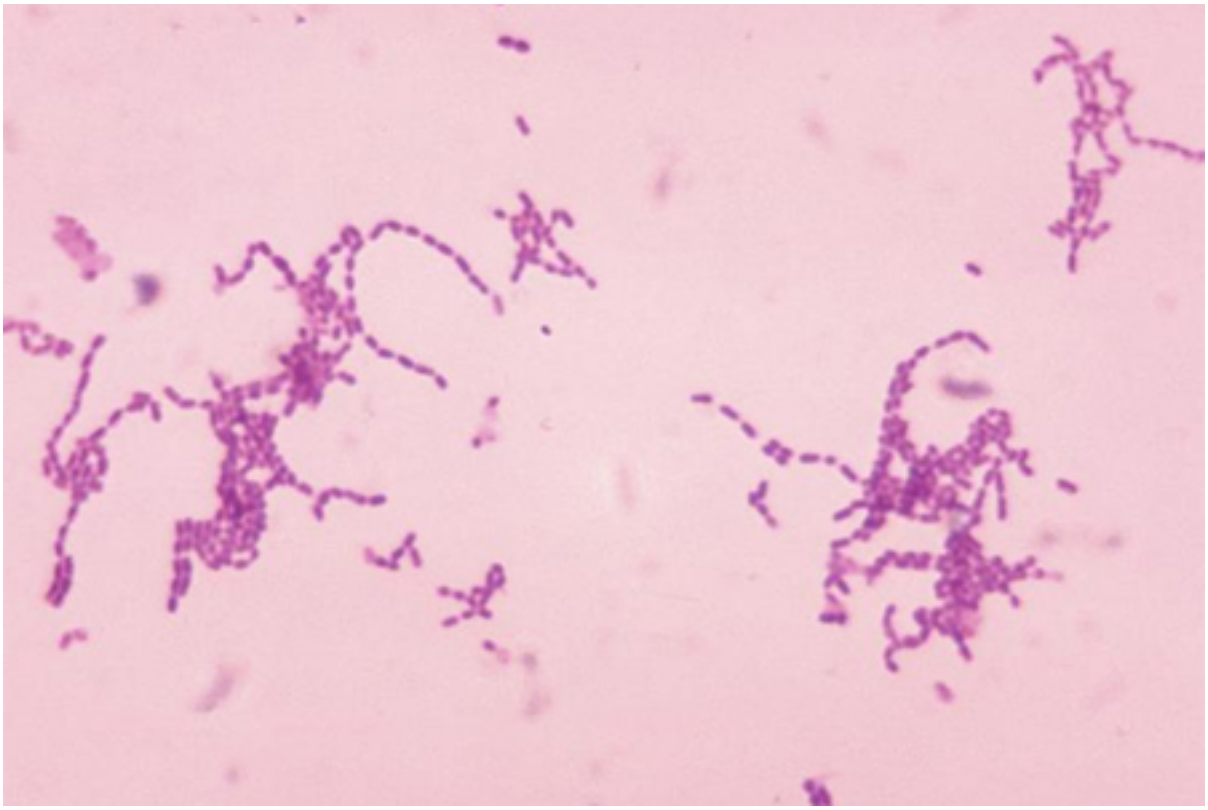


Figure 8: Photomicrograph of Gram-stained Streptococcus species bacteria

From the CDC Public Health Image Library

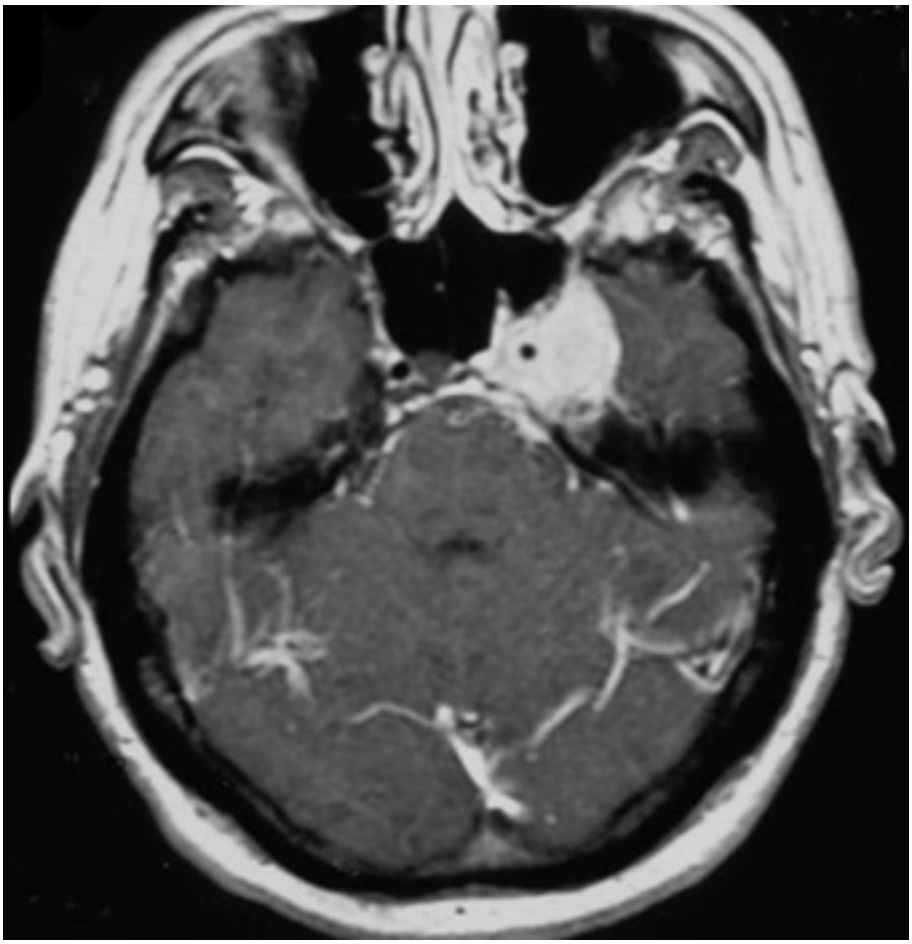


Figure 9: Meningioma: coronal contrast-enhanced image demonstrates meningioma in the cavernous sinus on the left side

From the personal collection of William T. Couldwell; used with permission

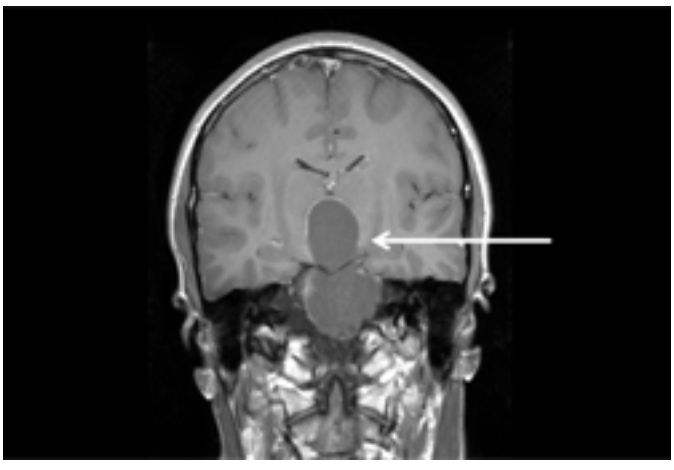


Figure 10: Craniopharyngioma: coronal postcontrast MRI

From the personal collection of Marc C. Chamberlain; used with permission

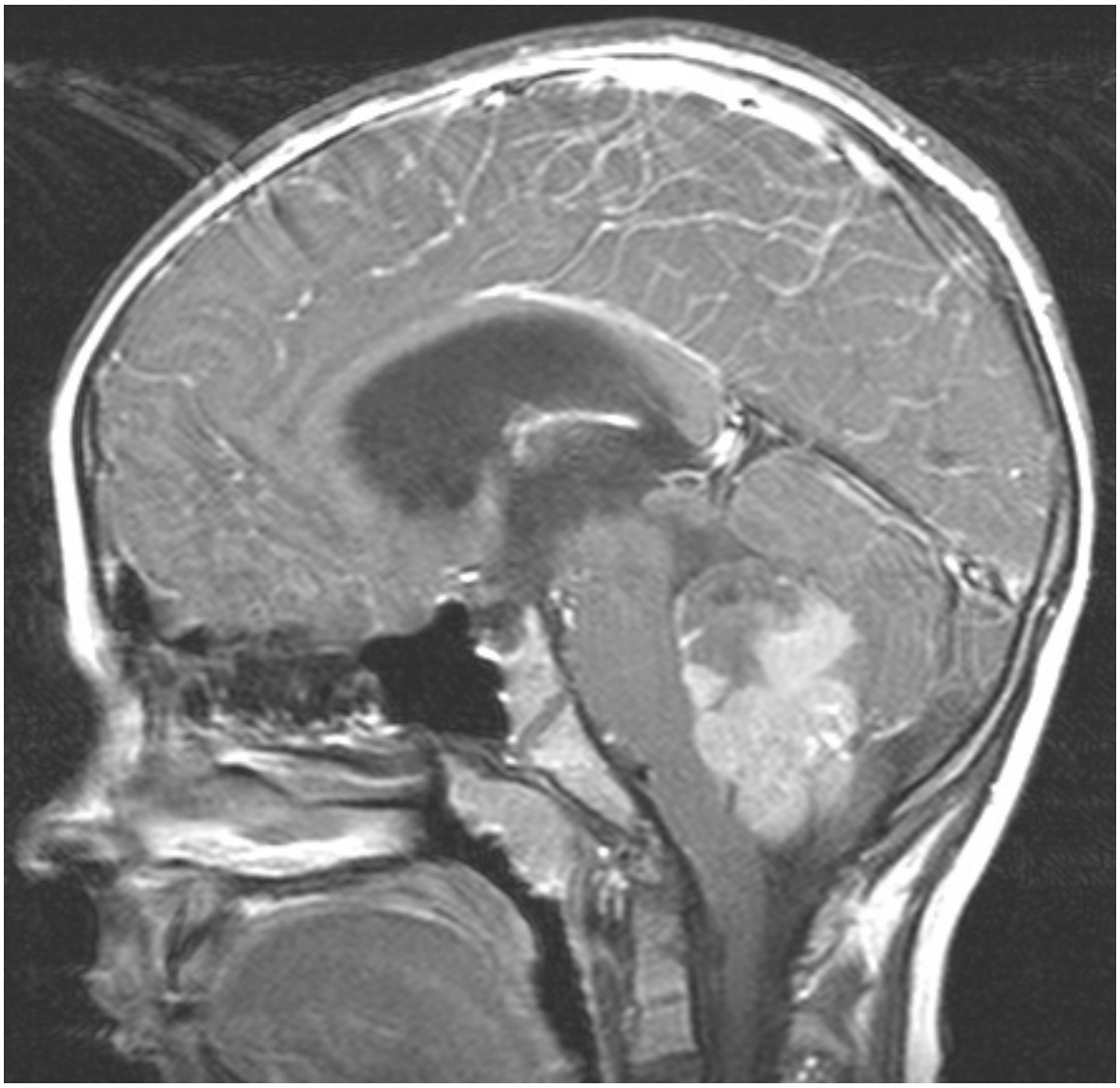


Figure 11: Medulloblastoma: sagittal view MRI showing an avidly enhancing solid and cystic lesion filling the fourth ventricle; obstructive hydrocephalus present

From the collection of Peter B. Storm; used with permission

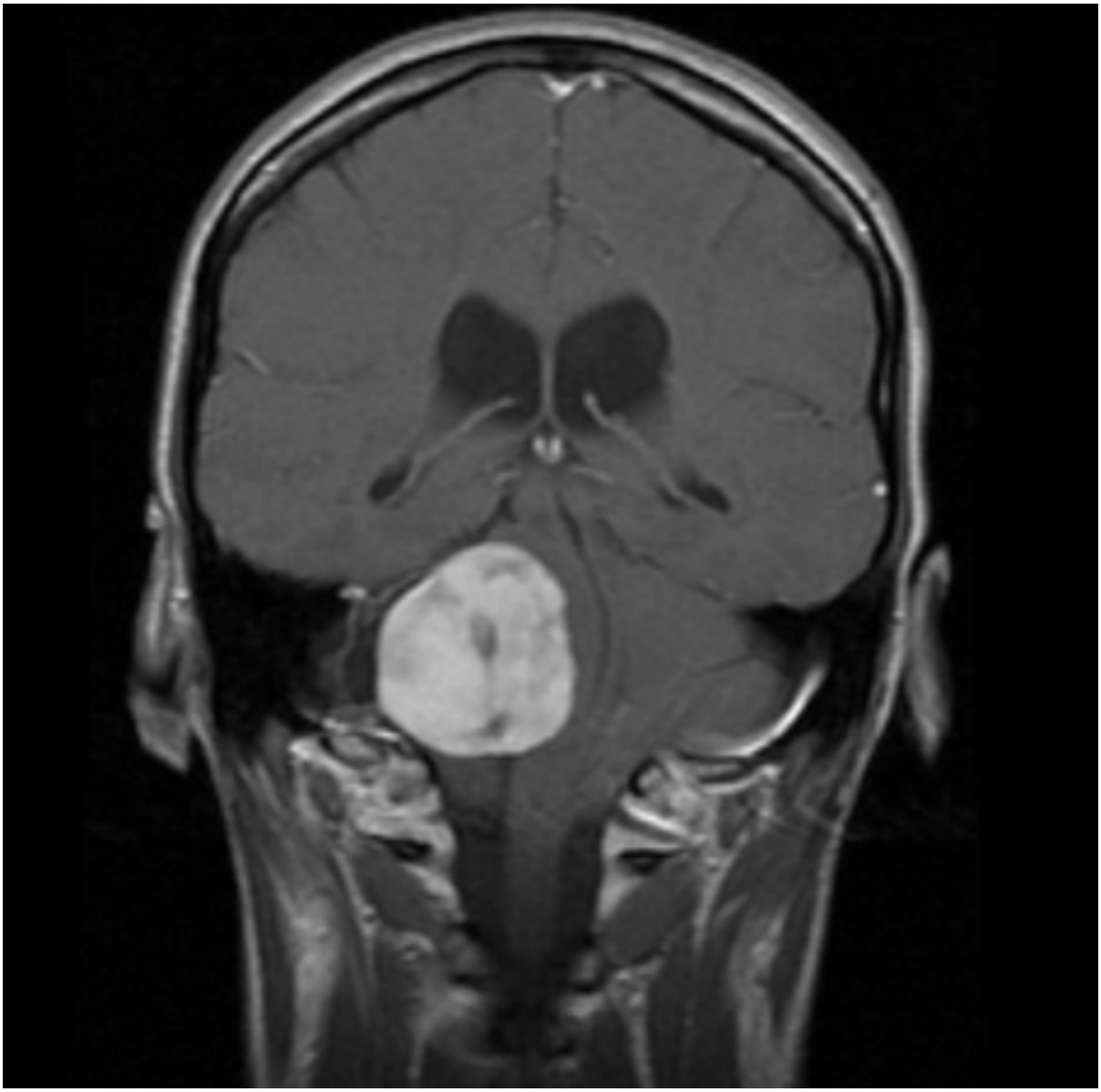


Figure 12: Acoustic neuroma: coronal postcontrast MRI

From the collection of Ryojo Akagami; used with permission

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

G. Bryan Young, MD, FRCPC

Emeritus Professor of Neurology
University of Western Ontario, ON, Canada
DISCLOSURES: GBY declares that he has no competing interests.

// Peer Reviewers:

Paul Vespa, MD

Professor of Neurology and Neurosurgery
Director of Neurocritical Care, David Geffen School of Medicine at University of California, LA
DISCLOSURES: PV declares that he has no competing interests.

Steven Laureys, MD, PhD

Department of Neurology
Liege University Hospital, Head, Coma Science Group, Senior Research Associate, Belgian National Funds for Scientific Research, Cyclotron Research Centre, University of Liege, Belgium
DISCLOSURES: SL is the author of one of the papers cited in this article.

Eelco F. Wijdicks, MD, PhD

Professor of Neurology
Mayo Clinic, Rochester, MN
DISCLOSURES: EFW declares that he has no competing interests.