Coma, Disorders of Consciousness, and Brain Death

17

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Introduction

Consciousness is the state of full awareness of the self and one's relationship to the environment [1]. Classical neurological thought makes a distinction between the content of consciousness and the level of consciousness. The content of consciousness includes specific modalities, such as symbolic language, or memory. The level of consciousness is the degree to which a person can maintain a waking state, termed arousal, and their awareness of the environment. It is these disorders of the level of consciousness that is the focus of this chapter.

Historically, clinicians have classified and organized disorders of the level of consciousness based on clinical findings at the bedside. Clinical syndromes include encephalopathy, minimally conscious states, unresponsive wakefulness syndrome, and coma (Table 17.1). Physicians in emergent and critical care settings are required to assess and manage patients with various disorders of consciousness, ranging from encephalopathy to coma, and to distinguish these living patients from those with brain death. The adept physician is able to use the neurological exam in conjunction with a variety of diagnostic modalities to define the specific syndrome and cause of their patient's presentation. Accurate and competent assessment of these disorders, and an understanding of the neuroanatomical and neurophysiological mechanisms underlying them, is crucial for guiding treatment plans and prognostication.

On the extreme end of the disorders of consciousness is coma. Coma is defined as a state of complete unresponsiveness to external or internal stimuli. It is characterized by a failure of arousal and consciousness: patients in coma have no spontaneous eye opening, do not arouse to sensory stimuli, have no sleep-wake cycles, and do not follow any commands. However, they do have at least one brainstem reflex preserved. In some cases, there may be preservation of complex brain-derived reflexes with inputs from the cortical and subcortical structures of the brain. Coma results from severe damage to the brainstem, thalamus, and/or both cerebral hemispheres simultaneously. Unresponsive wakefulness syndrome (UWS), previously known as the persistent vegetative state, is a syndrome where patients are awake (eyes open, or other evidence of a sleep-wake cycle such as EEG patterns) but remain otherwise unresponsive, showing only reflexive movements [2]. Minimally conscious state is a syndrome where the patient is awake but in which there is only evidence of a minimal

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Table 17.1 Level of consciousness

	Sleep-wake cycles	Episodes of awareness	Ability to track a visual stimulus;	Ability to follow commands
Disorder of consciousness				
Coma	Absent	Absent	Absent	Absent
Unresponsive Wakefulness syndrome	Present	Absent	Absent	Absent
Minimally conscious state	Present	Present but frequency can vary from rare to frequent	Present	Can vary in degree
Normal Consciousness	Present	Present	Present	Intact
Mimics of consciousness				
Locked-in state	Present	Present	Can track using vertical eye movements	Can only be detected at the bedside using vertical eye movements
Covert Consciousness	Present	Present	Absent	Can only be detected with tasked-based MRI or EEG

awareness of self or environment [3]. Recently, there has been a further subclassification of minimally conscious state based on the presence of language: MCS− and MCS+. Patients with MCS+ have at least one of the following features: command following, intelligible verbalization, or intentional communication [4]. This distinction was made to facilitate research in prognostication.

Akinetic mutism is a rare form of arousal failure, characterized by an emotionless, frequently motionless state with intact visual tracking, and occurs commonly due to lesions in the bilateral anterior cingulate gyri. Encephalopathy is characterized by failure of normal arousal, in which the level of arousal fluctuates. Patients with encephalopathy have an abnormal level of consciousness and arouse inconsistently to internal and sensory stimuli in contrast to patients in coma who arouse to neither internal nor external stimuli. Encephalopathy, like coma, results from damage to the brainstem, thalamus, or both cerebral hemispheres, but the damage is less severe. The neuroanatomical localization of arousal failure to the brainstem, thalamus, or both cerebral hemispheres is the most important principle to consider in the approach to a comatose or encephalopathic patient. Localization of the brain injury producing the arousal failure leads to efficient and timely treatment of the disease.

Mimics of Disorders of Consciousness

Great care must be taken by the clinician to distinguish true disorders of consciousness with mimics such as the locked-in syndrome and covert consciousness. The locked-in syndrome is where a patient with intact consciousness is only able to communicate with an observer through vertical eye movements or blinking. This occurs due to pontine injury that prevents motor signals from controlling any other movements in the body. Since 2005, further studies have identified syndromes of covert consciousness. These patients are conscious in that they are alert and aware but lack the ability to communicate with an observer. Evidence of their consciousness is gathered using task-based functional MRI which shows evidence of activity in specific brain regions when patients are presented with a task [5] or using resting and task-based continuous EEG which can identify patterns of activity associated with conscious states. From an ethical perspective, there is an imperative to identify these patients because there is the potential to discover and provide a possible means of reliable communication which can dramatically impact the patient's quality of life, as well as to possibly restore at least some element of the patient's autonomy and capacity for decision-making [6, 7]. Furthermore, patients with covert consciousness, as identified by EEG analysis, have

a significantly better prognosis compared to those patients truly in comatose states. For instance, in a study of 104 unresponsive patients, assessed to be comatose at the bedside, 16 were detected to have brain activation by EEG after a median of 4 days after injury, and those patients had a four and a half times greater odds of achieving a state where they could function independently for 8 h on a 12-month follow-up [8]. Appropriate identification of these patients can thereby significantly change prognosis and guide decision-making by proxy decision-makers and clinicians. At the time of writing this chapter, the use of these advanced functional diagnostic tests and analysis to identify covert consciousness is not widespread and is usually done as part of research protocols at certain centers. More research is likely needed to incorporate the use of these technologies in the ICU and clinical setting.

Finally care must be taken to distinguish between brain death and coma. Brain death is not a disorder of consciousness because the person is no longer alive. Brain death is characterized by the irreversible absence of all clinical brain activity after exclusion of toxic or metabolic confounders, such as drug overdose, general anesthesia, or hypothermia. The specific criteria and variation in determining brain death are discussed in the Brain Death section of this chapter.

Anatomy and Pathophysiology of Disorders of Consciousness

As a general rule, disorders of arousal and consciousness result from significant injury to the upper brainstem, thalamus, thalamocortical projections, or bilateral cortices. The anatomy and physiology of these structures as they pertain to arousal are described below. Figure 17.1 schematically approximates these arousal systems neuroanatomically. Table 17.2 summarizes the components of each of the arousal systems.

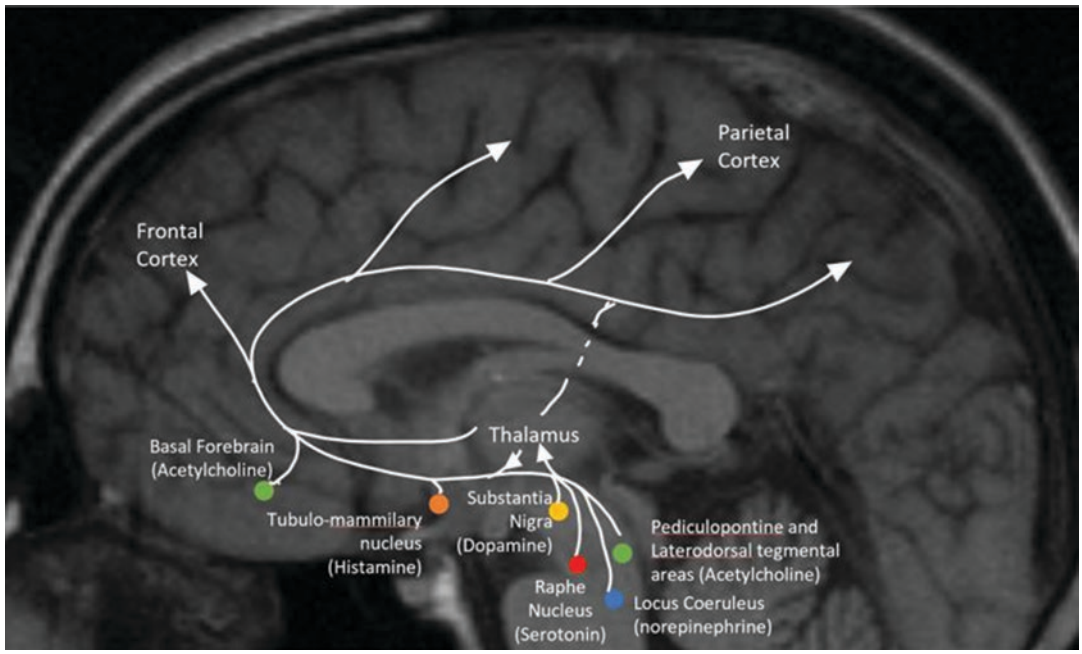

Fig. 17.1 Some of the key areas of the brain important to maintaining arousal are shown overlayed on a sagittal MRI image of the brain. Neurons from different brainstem nuclei send excitatory signals, using different neurotransmitters, to the targets in the thalamus, cortex, and subcortical white matter that ultimately lead to arousal. The arousal nuclei that are in the brainstem are in turn innervated by orexin neurons in the lateral hypothalamus for further modulation. Cholinergic neurons from the pedunculopontine and laterodorsal tegmental area (shown in green) activate targets in the thalamus as well as the forebrain. Serotonergic neurons from the dorsal raphe nuclei (red), histaminergic neurons in the tuberomammillary nucleus (orange), dopaminergic neurons from the substantia nigra and ventral tegmental area (yellow), and adrenergic neurons from the locus coeruleus (blue) send excitatory inputs to many cortical and subcortical targets

Table 17.2 Arousal systems

Brainstem arousal systems
Reticular activating system (RAS)
Pedunculopontine tegmental and laterodorsal nuclei (PPT/LDT)
Locus coeruleus (LC)
Substantia nigra pars compacta and ventral tegmental area (SNPC-VTA)
Raphe nucleus (RN)
Thalamic arousal systems
Specific thalamocortical system
Nonspecific thalamocortical system
Basal forebrain arousal systems
Substantia innominata
Nucleus basalis of Meynert
Diagonal band of Broca
Magnocellular preoptic nucleus
Median septum
Globus pallidus
Hypothalamic arousal system
Posterior hypothalamus
Anterior hypothalamus

Arousal Systems

Arousal or vigilance is mediated by a complex interaction of cortical and subcortical networks. Cortical activation is required for arousal and awareness, but anatomic and physiological data suggest that the cortex does not contain an intrinsic mechanism for the generation and maintenance of arousal [9, 10]. As such, a number of subcortical networks participate in the generation of arousal [11]. These networks include arousal systems located in the brainstem, thalamus, basal forebrain, and hypothalamus. Signals from peripheral sensory organs, such as the eyes, ears, or skin, are detected by sentinel arousal systems within the brainstem, which in turn excite thalamocortical neurons. Sensory transmission within the thalamus also directly excites thalamocortical neurons. Thalamocortical neuron excitation promotes cortical excitation, which is supportive of arousal. The hypothalamus and basal forebrain are also important in arousal, although the precise identification of their role is still under investigation. These systems are summarized in the sections that follow.

Brainstem Arousal Systems

The brainstem arousal systems comprise the reticular activating system (RAS), the pedunculopontine tegmental and laterodorsal (PPT/LDT) nuclei, the locus coeruleus, the substantia nigra pars compacta, and the midline raphe nuclei. These nuclei are located in disparate anatomical sites in the brainstem, but each is optimally positioned to broadly send and receive information. Because of their anatomical positioning and broad rostral projections, these nuclei may serve as sentries for the arousal system. The RAS is the best studied of these nuclei and is representative of the structure and function of these systems. The RAS comprises neurons in core nuclei located near the cerebral aqueduct of the midbrain and near the fourth ventricle in the pons [12, 13]. These neurons are interspersed in a web-like reticulum between the ascending and descending fibers, which comprise the motor and sensory tracts as they traverse the brainstem. The RAS neurons have long dendrites that interdigitate those fibers and are thus optimally situated to integrate information from a wide variety of sources, including sensory input from visual, somatosensory, auditory, and vestibular systems, as well as sensory and motor output from the cerebral cortex, thalamus, and basal ganglia [14, 15]. Ascending arousal signals from the reticular formation to the forebrain are conveyed through two systems: the dorsal system that traverses the thalamus and transmits diffusely to the cortex through thalamocortical projections and the ventral system, which comprises the basal forebrain and hypothalamus, that acts as key relay components.

Thalamic Arousal Systems

The thalamus is crucial for achieving and maintaining arousal through its connections with the cortex. The thalamus receives and sends data to and from virtually all central nervous system structures. Functionally, thalamic nuclei have been classified into “specific” and “nonspecific” thalamocortical systems through which the thalamus projects to the cortex [16]. “Specific” thalamocortical projections convey information within the sensory, visual, auditory, or motor systems, which have precise neuroanatomical localizations within the cortex and thalamus, and include such thalamic nuclei as the medial and lateral

geniculate nuclei and the group of ventral nuclei. In contrast, "nonspecific" thalamocortical projections transmit information from multiple subcortical nuclei, including the reticular nuclei, dorsal raphe, PPT/LDT nuclei, locus coeruleus, basal forebrain, and hypothalamus, to multiple cortical regions. Nonspecific thalamocortical projections originate from midline, medial, and intralaminar groups of thalamic nuclei, which are located in the central thalamus. Contrary to initial reports, these central thalamic nuclei actually have a specific neuroanatomical localization, which has drawn into question their identification as "nonspecific" [17]. Because of their connection with the cortex, each of the thalamocortical projection systems can play a role in cortical activation.

Hypothalamic and Basal Forebrain Arousal Systems

The hypothalamus plays a vital role in both arousal and sleep generation. Based on studies in cats, the posterior hypothalamus appears to be the most important hypothalamic center for arousal behaviors, whereas the anterior hypothalamus and hypothalamic–mesencephalic junction promote sleep [18]. Studies of the cellular physiology mediating the influence of the hypothalamus on arousal and vigilance are ongoing. Hypothalamic nuclei comprise many types of neurons, including histaminergic and peptidergic neurons, which produce orexins. Histaminergic neurons are found primarily in the tuberomammillary nucleus and posterior hypothalamus and can influence arousal via projections to the anterior hypothalamus, the dorsal raphe nuclei, the mesopontine tegmentum, the thalamus, the substantia innominata, and directly to the cortex [19]. Histaminergic neurons can influence the firing mode of thalamocortical neurons depending on the relative distribution and activation of distinct histamine receptors (H1R and H2R), which each has different mechanisms of postsynaptic activity [20]. Orexins (hypocretins) are neuropeptides that promote arousal; they project to almost every brain region involved in the regulation of wakefulness; and they fire most strongly during active wakefulness, high motor activation, and sustained attention [21]. Orexin-producing neurons, located within the posterior and lateral hypothalamic areas in the region of the fornix, are known to have widespread excitatory CNS projections, with densest projections to the locus coeruleus, in addition to other regions of the hypothalamus, the basal forebrain, the thalamocortical system, and to multiple brainstem nuclei [22, 23].

Basal forebrain structures include the substantia innominata, the nucleus basalis of Meynert, the diagonal band of Broca, the magnocellular preoptic nucleus, the medial septum, and the globus pallidus [24]. Neurons in the basal forebrain are a major source of acetylcholine release throughout the brain and thus play a major excitatory role in cortical activation and arousal [25]. However, unlike thalamocortical neurons, intact basal forebrain activity is not required for arousal: destruction of the basal forebrain in cats does not abolish cortical activation [26]. The basal forebrain's exact contribution to arousal is still under investigation.

Approach to Patient Presenting with Acute Coma

A patient presenting with an acutely unresponsive state is treated as a medical emergency. The etiologies of an acute unresponsive state are broad. Some are rapidly reversible; others require emergent management to prevent or minimize permanent injury to the brain. A structured systematic approach can help guide the clinician to determine the cause and emergently treat their patient. In this section, we will discuss the differential diagnosis for a patient presenting with acute coma; describe a systematic step-by-step approach to diagnosis; and then describe the emergent management of these patients with an emphasis on the "brain code," which is the management of cerebral herniation.

Etiologies of Acute Coma

Disruption or dysfunction in the pathways of consciousness are the final common pathway for the syndrome of coma. This can happen either through structural lesions that disrupt the path-

ways of consciousness or nonstructural dysfunction that prevents the pathways from working. A helpful mnemonic for considering all possible etiologies in neurological disorders, especially for neurological disorders such as coma with a myriad of potential etiologies, is "VITAMINS C/D," which stands for *v*ascular, *i*nfection, *t*rauma, tumor, *a*utoimmune/inflammatory, *m*etabolic, *m*edications, *i*ntracranial pressure (high or low), *n*eoplasms, *s*eizures, *c*erebrospinal fluid disorders (hydrocephalus), and *d*evelopmental/congenital anomalies. For coma, there are etiologies in each of these categories. Etiologies classified using this classification are summarized in Table 17.3.

Vascular injuries, such as focal cerebral ischemia due to ischemic stroke, global cerebral ischemia due to cardiac arrest, intracerebral hemorrhage, subarachnoid hemorrhage, or vasculitis, can cause disorders of arousal by directly damaging the brainstem or thalamus. Also, mass effect caused by cerebral edema after vascular injuries can lead to elevated intracranial pressure, obstructive hydrocephalus, and herniation, which can in turn damage the arousal system through direct compression. Vascular injuries tend to occur abruptly and, in the case of ischemic stroke and intracerebral hemorrhage, are likely to present with neurological dysfunction localizable to brainstem or thalamic injury when they also affect the level of consciousness. Basilar migraine, a rare migraine subtype, is an unusual cause of acute coma and may be suspected based on a history of headaches, but it is usually a diagnosis of exclusion after ruling out other more sinister diagnoses including basilar artery stroke. Posterior reversible encephalopathy syndrome (PRES) is an acute neurotoxic syndrome that may present with disorders of consciousness including coma and is also associated with seizures, visual disturbances, and focal neurological deficits [27, 28]. Common triggers include blood pressure fluctuations, renal failure, eclampsia, exposure to immunosuppressive or cytotoxic agents, and autoimmune disorders, and PRES is typically diagnosed through classic radiographical findings that show subcortical vasogenic edema [29].

Infections, such as meningitis, encephalitis, or abscess, can affect the level of consciousness through at least two mechanisms. The infectious process and associated inflammatory process can impair cortical activity diffusely through changes in blood flow, altered CSF dynamics, and cerebral edema. Alternatively, the infection itself may directly involve the cells in the arousal system. Infections can present acutely, subacutely, or chronically, may be associated with fever and leukocytosis, and usually cause an abnormal cerebrospinal fluid. The differential diagnosis for the various organisms that cause meningitis/encephalitis is beyond the scope of this chapter.

Trauma frequently causes failure of arousal either by direct traumatic injury to the arousal system or through compression of the arousal system due to concomitant cerebral edema. Diffuse axonal injury can also lead to slowed or decreased signal transmission throughout the subcortical white matter and may result in a variety of disorders of consciousness. Trauma can also cause subdural hematomas, typically through shearing of the dural bridging veins, which over time can cause compression, high ICP, and resultant coma. Trauma can also cause epidural hematomas, typically caused by damage to a meningeal artery, presenting with initial loss of consciousness, followed by a lucid period, and then subsequent rapid decline. Trauma is usually suggested by the history and presentation and evidence of trauma on physical examination.

Autoimmune or inflammatory etiologies can cause failure of arousal through mechanisms similar to infection. The clinical presentation may be identical to infection, except that there is no evidence of an infectious etiology on cultures. Numerous new antibodies associated with distinct syndromes of autoimmune encephalitis have been characterized, and this continues to be an ongoing research endeavor. Paraneoplastic autoimmune encephalitis is part of this subset, and investigation for neoplasm should occur if a noninfectious encephalitis is high on the differential. In addition to primary autoimmune encephalitis, systemic autoimmune diseases can also have CNS manifestations with presentations of coma through a variety of mechanisms such as

Table 17.3 Non-exhaustive summary of causes of acute coma, sorted using the VITAMINS C mnemonic

Vascular	Ischemic stroke/hypoperfusion Intracerebral hemorrhage Subarachnoid hemorrhage Cardiac arrest Vasculitis Posterior reversible encephalopathy syndrome [48] Basilar migraine
Infection	Meningitis Encephalitis Abscess
Trauma	Direct damage to key structures from trauma Diffuse axonal injury Subdural hematoma Epidural hematoma
Autoimmune/inflammatory	Autoimmune meningitis Autoimmune encephalitis Systemic autoimmune diseases with CNS involvement Posterior reversible leukoencephalopathy syndrome
Metabolic derangements	Hypoxia Hypoglycemia Hyperglycemia (diabetic ketoacidosis, hyperosmolar nonketotic hyperglycemia) Hyponatremia Osmotic demyelination syndrome (from rapid correction of hyponatremia) Thyroid dysfunction: myxedema coma, thyrotoxicosis Pituitary apoplexy Adrenal crisis Uremia Hypercarbia Hyperammonemia Hypo- and hypercalcemia
Medications/drug toxicities	Opioid intoxication/overdose Gabapentinoids Propofol Sedative hypnotics (alcohol, benzodiazepines, barbiturates, baclofen, and clonidine) Cocaine washout syndrome Carbon monoxide (CO) poisoning Tricyclic antidepressant overdose Organophosphate poisoning Cefepime neurotoxicity [48] Serotonin syndrome Neuroleptic malignant syndrome Antiepileptic drugs
Intracranial pressure	High ICP
Neoplasm	Benign and malignant cranial tumors causing mass effect/edema Carcinomatous meningitis
Seizures	Nonconvulsive status epilepticus from various causes Post-ictal state
CSF disorders	Hydrocephalus (communicating or non-communicating)
Developmental/congenital anomalies	

inflammation of cerebral tissue, mass lesions in the CNS, meningitis and encephalitis, and vasculitis. In these diseases, serum markers of inflammation are elevated, such as ESR, ANA, or ANCA.

Metabolic derangements and medications are among the most common causes of arousal failure and can be diagnosed by history or laboratory testing. Common metabolic derangements that can alter consciousness are hypo- and hyperglycemia (in the case of diabetic ketoacidosis or hyperosmolar nonketotic hyperglycemic syndrome), hypo- or hypernatremia, hyperuremia, hypercarbia, hypoxia, hyperammonemia, and hypercalcemia. Endocrine disorders can also present with coma. This includes thyroid disorders such as myxedema coma (severe untreated hypothyroidism) and thyrotoxic storm; pituitary apoplexy which is characterized by sudden hemorrhage or infarction of the pituitary gland; acute adrenal crisis either from primary Addison's disease, a secondary disorder or glucocorticoid-induced [30]. Osmotic demyelination syndrome, which includes central pontine myelinolysis, is typically caused by rapid correction of hyponatremia and can cause damage to different parts of the brain but most typically causes pontine dysfunction. This can lead to locked-in-syndrome, a mimic of coma, that is discussed in more detail in the Chronic Coma section, and should be screened for on neurological assessment.

Medications and toxins that can lead to a depressed level of consciousness include, but are not limited to, opioids, gabapentinoids, antiepileptic medications, sedative hypnotics (including alcohol, benzodiazepines, barbiturates, baclofen, and clonidine), stimulant washout syndromes (such as cocaine), carbon monoxide (CO) poisoning, and toxin-induced brain-death mimickers (such as tricyclic antidepressant overdose, organophosphate poisoning, and cefepime neurotoxicity) [31]. The elderly and patients with preexisting brain injuries are particularly sensitive to both metabolic derangements and medications which alter the level of consciousness [32]. Serotonin syndrome is a potentially life-threatening syndrome caused by overdose of serotoninergic drugs and can present with coma, along with autonomic hyperactivity including tachycardia and hyperthermia and neuromuscular abnormalities such as clonus, hyperreflexia, and rigidity. A wide range of drug classes can contribute to serotonin syndrome, including but not limited to a broad range of antidepressant classes, anxiolytics, amphetamines, cocaine, tramadol, L-dopa, and lithium [33]. Neuroleptic malignant syndrome is another classic drug toxicity syndrome that can present with coma. It is characterized by altered mental status (including coma), generalized rigidity, hyperpyrexia, and dysautonomia and is typically caused by antipsychotic agent use [34]. The prompt identification of serotonin syndrome and neuroleptic malignant syndrome as distinct causes of coma is important because removal of the provoking drug and appropriate supportive care can dramatically alter the prognosis.

High intracranial pressure is often heralded by arousal failure and is most frequently caused by vascular lesions, infections, neoplasms, and hydrocephalus. High intracranial pressure can cause arousal failure through at least two mechanisms (1) cerebral herniation, where the pressure due to a lesion in a neighboring brain region forces brain tissue into the arousal system, and (2) diffusely elevated pressure causing diffuse cortical dysfunction.

Neoplasms can cause arousal failure if they grow directly into the arousal system, by compression of the arousal system after growth from a nearby focus or through derangement of the arousal system by vasogenic edema.

Seizures cause arousal failure through several mechanisms: (1) status epilepticus (convulsive or nonconvulsive) is associated with poor arousal; (2) during a single seizure or cluster of seizures, patients may be poorly arousable, depending on the size of the seizure focus; and (3) patients may fail to arouse reliably during the postictal period and after administration of sedating antiepileptic medications. Seizure as a cause of arousal failure is suggested by a history of epilepsy, witnessed tonic-clonic activity, or other seizure-related signs, such as tongue biting, and by an electroencephalogram with evidence of ongoing or recent seizure.

Cerebrospinal fluid disorders, mainly hydrocephalus, can compress and cause dysfunction in the thalamus and midbrain and can also lead to diffuse dysfunction of bilateral cortical projections. Hydrocephalus can be congenital or develop as a sequela of neoplasm, CNS infection, inflammatory disease, hemorrhage, or ischemic

stroke. In patients with congenital hydrocephalus, failure of a shunt device should also be considered a possible cause of arousal failure.

A Systematic Clinical Approach to the Patient Presenting with Acute Coma

Clinicians must have an organized and expedient approach involving time-sensitive diagnostic and therapeutic actions that often occur simultaneously. In order to codify and organize the approach to an acutely unresponsive patient in a stepwise manner, the Neurocritical Care Society first created the Emergency Neurological Life Support Recommendations in 2012 and have since revised them as of 2019. Figure 17.2, from the ENLS guidelines, offers a step-by-step approach for any emergent practitioner to follow when treating an acutely comatose patient [35].

In practice, multiple diagnostic tests and interventions occur simultaneously as new information is made available and as assessments continue. Nevertheless, clinicians should use an organized approach, as much as is feasible, in evaluating and treating patients with acute coma.

ACLS and ATLS Evaluation As per the algorithm above, the initial assessment of all patients with critical illness should focus on the ABCDs (airway, breathing, circulation, and defibrillation) of Advanced Cardiac Life Support (ACLS) and Advanced Trauma Life Support (ATLS). A full description of ACLS and ATLS guidelines is beyond the scope of this chapter. Relevant materials can be obtained from their respective sponsoring organizations with the American Heart Association for the ACLS and the American College of Surgeons for the ATLS. If trauma or c-spine injury cannot be ruled out, stabilization of the c-spine should occur early so as to prevent any exacerbation of spinal cord or nerve injury.

Rapid Neurological Assessment The next step is to perform a rapid neurological assessment. The purpose of this rapid screen is to identify potential neurological catastrophes which must be intervened upon emergently, such as cerebral herniation or a stroke syndrome. A rapid neurological assessment includes determination of level of consciousness, evaluation for pupil asymmetry and light reactivity, brainstem reflexes, and evaluation of motor function. If the rapid neurological assessment suggests cerebral herniation, impending herniation, or intracranial hypertension, then medications to reduce intracranial pressure should be emergently initiated

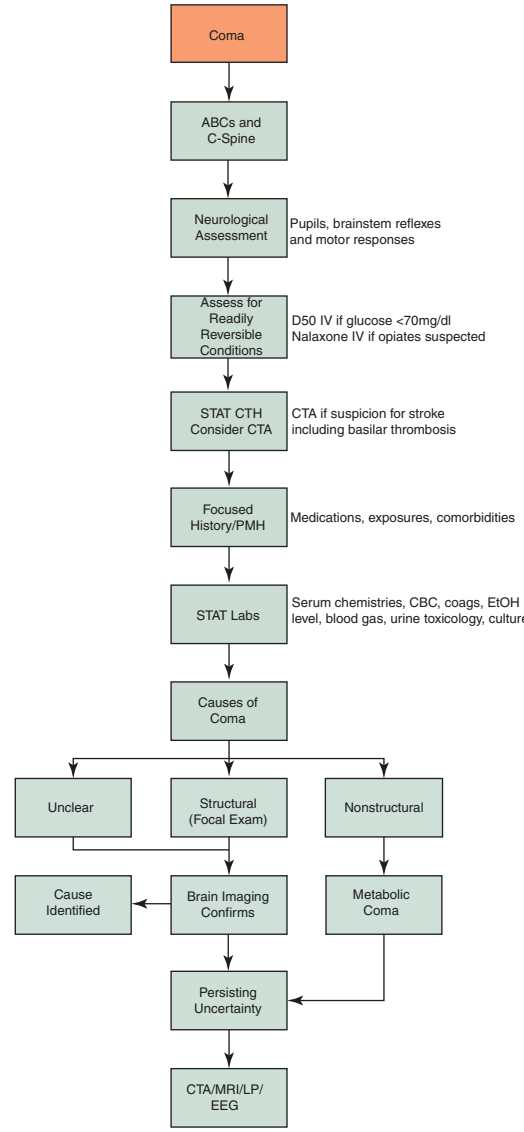

Fig. 17.2 Suggested algorithm from ENLS for approach to acute coma. (Reproduced from Venkatasubramanian et al. [35], with permission from Springer Nature)

("brain code"; see "Emergent Therapies for Arousal Failure" section). Concurrent presence of hypertension, bradycardia, and hyperventilation comprises the "Cushing's reflex," which is also seen frequently in patients with intracranial hypertension. This triad is a physiological response that can maintain cerebral perfusion in the setting of high intracranial pressure through systemic hypertension, increased cardiac filling time, and decreased cerebral blood volume (through hyperventilation-induced arteriolar vasoconstriction) [36]. Other helpful observations in the neurological exam include observation for any rhythmic movements of the body or of the eyes, or gaze deviation, that may be suspicious for ongoing seizures.

Standardized scoring scales for consciousness such as the Glasgow Coma Scale and the FOUR Score (Tables 17.4 and 17.5) are commonly used in emergent settings to allow for rapid communication of the patient's status among providers and allow for efficient algorithmic decision-making. The Glasgow Coma Scale (GCS) is used extensively in acute settings to assess level of consciousness. The table below shows how points are assigned in the scale. When patients cannot speak due to an endotracheal tube or tracheostomy, the GCS score is annotated with a "T." For instance, a patient with endotracheal intubation, no eye opening, and a best motor response of extensor posturing to pain will have a GCS score of 4 T. The GCS is limited as it does not account for brainstem dysfunction, hemiparesis, or aphasia. This means that patients with the same GCS score could have varying clinical presentations from very different etiologies. The Full Outline of UnResponsiveness (FOUR) Score includes eye responses, motor responses, brainstem reflexes, and respiratory pattern and therefore incorporates more detailed information that could be extremely clinically useful [37]. For example, using the FOUR score, one can identify a patient who has locked-in syndrome, and is actually conscious but only able to communicate through eye movements. The FOUR score has been validated in a variety of clinical settings, including the ICU setting [38].

Table 17.4 Glasgow Coma Scale

Eye examination
4 – Eyes open spontaneously
3 – Eyes open to voice
2 – Eyes open to pain
1 – No eye opening
Verbal response
5 – Oriented
4 – Confused
3 – Inappropriate words
2 – Incomprehensible sounds
1 – No verbal response
Motor examination
6 – Obeys commands
5 – Localizing pain stimuli
4 – Withdrawal from painful stimuli
3 – Flexor posturing to painful stimuli
2 – Extensor posturing to painful stimuli
1 – No motor response
Total score: 3 (lowest) to 15 (highest)

Table 17.5 Four score scale

Eye response
4 – Eyelids open or opened, tracking or blinking to command
3 – Eyelids open spontaneously, but not tracking nor blinking to command
2 – Eyelids closed but open to loud voice
1 – Eyelids closed but open to pain
0 – Eyelids remain closed even with pain
Motor response
4 – Thumbs up, fist or peace sign (to command)
3 – Localizes to pain
2 –Flexion response to pain
1 – Extension response to pain
0 – No response to pain or generalized myoclonus
Brainstem reflexes
4 – Pupillary light reflex and corneal reflexes present
3 – One pupil wide and fixed
2 – Either the pupillary light reflex or the corneal reflex is absent
1 – Both the pupillary light reflex and corneal reflex are absent
0 – Absent pupil, corneal, and cough reflex
Respiration
4 – Regular breathing pattern
3 – Cheyne–Stokes breathing pattern
2 – Irregular breathing
1 – Triggers ventilator or breathes above the set ventilator rate
0 – Apnea or breathing at the set ventilator rate only
Total score: 0 (lowest) to 16 (highest)

Although the ENLS algorithm makes a distinction between the steps of emergent medical and emergent neurological assessments, there are

a number of special considerations in patients with emergently critical neurological illness that interplay between the two.

Comatose patients (GCS <9) are often thought to have lost the ability to "protect their airway." On examination, comatose or encephalopathic patients are often snoring loudly or "gurgling." This is because their neurological injury decreases their normal upper airway muscular tone and increases upper airway resistance. This makes spontaneous ventilation more difficult and increases the risk of aspiration. In general, comatose patients (GCS <9) undergo emergent endotracheal intubation for airway protection to facilitate ventilation and minimize the risk of aspiration and pulmonary complications. Until intubation and mechanical ventilation are achieved, patients should be supported for both ventilation and oxygenation using bag mask ventilation with adequate FiO2 and, if needed, an oral or nasopharyngeal airway to maintain airway patency. During bag mask ventilation and after endotracheal intubation, initial goals of normocapnia ($PaCO_2$ 35–39 mmHg) and normal oxygenation (SaO_2 95–100% or PaO_2 > 80 mmHg) should be set. After identification of the neurological insult, these goals may be modified.

Patients with critical neurological illness can present with a wide range of cardiac rhythms and blood pressures. Again, standard ACLS guidelines take immediate precedence in the emergent assessment of a comatose patient. Therefore, unstable cardiac rhythms and very low blood pressures (SBP <80 mmHg) should be assessed using the ACLS guidelines. At this stage in the emergent assessment, the precise etiology of the neurological injury may still not be known, although the history and examination may point to a likely cause. In the comatose patient who does not require ACLS resuscitation, blood pressure should be initially evaluated with consideration of all possible etiologies of critical neurological illness. Blood pressure goals are normally set to a fairly broad range until the etiology of the neurological injury is identified (usually in parallel to establishing adequate ventilation). At this stage in the assessment, the clinician should initially employ a broad blood pressure goal range in order to seek a balance between treating the neurological injury and avoiding iatrogenic exacerbation of the injury. For example, patients with acute ischemic stroke may require higher blood pressures to maintain perfusion of ischemic brain territories, whereas patients with intracerebral or subarachnoid hemorrhages will ultimately require lower blood pressures to prevent worsening of the hemorrhage [39, 40]. A broad blood pressure range also helps guide the use of anesthetic agents during endotracheal intubation, which may result in precipitous swings in blood pressure.

Evaluation for Hypoglycemia and Drug Toxicity All acutely comatose patients should have a rapid glucose test, either in the field or on arrival to the emergent setting, as hypoglycemia can cause coma and can result in permanent brain injury if not rapidly corrected. If blood glucose is less than 70 mg/dL, dextrose should ideally be administered intravenously. If the patient's history is suspicious for someone with malnutrition (history of alcohol dependence, cancer, bariatric surgery, eating disorders), if their appearance is cachectic, or if the relative history is unknown, then intravenous thiamine should be given prior to dextrose. These patients are at a higher risk for thiamine deficiency, and starting an intravenous glucose infusion without first replenishing thiamine can result in acceleration of damage to structures in the brain. If the patient's history or exam is suspicious for opioid toxicity, administer naloxone intravenously or intranasally and repeat as needed. Clinical signs suspicious of opiate toxicity include depressed respirations (apnea or bradypnea) and small pupils. As part of the initial survey, making note of any marks in the extremities or torso suspicious for intravenous injection should also be done. If patients have taken a longer acting opioid such as hydromorphone, repeated doses of naloxone may be needed.

Initial Diagnostic Tests

After initial stabilization of ABCs, securement of the c-spine, and intervening for emergencies such

as cerebral herniation or status epilepticus, the next step is to get an emergent noncontrast computed tomography (CT) scan of the head, possibly along with a CT angiogram (CTA) of the head and neck and a CT perfusion (CTP) scan, to look for any structural causes of coma that may need emergent intervention. A CT head without contrast can help identify intracranial hemorrhage, evolving ischemic strokes with edema, mass effect from edema or lesions, hydrocephalus, extra-axial fluid collections, and subarachnoid hemorrhage among other structural causes. The need for a rapid CT is evident from the fact that further management does change significantly based on what is found on the head CT. For instance, identification of hydrocephalus makes CSF decompression through the placement of an intraventricular catheter of paramount importance. Similarly, identification of an aneurysmal subarachnoid hemorrhage triggers the need for stricter BP control, a neurovascular workup, and ultimate procedural securement of the aneurysm either through clipping, coiling, or a flow diverter device. A CTA head/neck along with a CT perfusion scan can help identify possible basilar occlusion and/or other large vessel occlusions that may be amenable to intravenous tissue plasminogen activator treatment (iv tPA) or intraarterial thrombolysis. A CTA head/neck could also identify possible vascular malformations or aneurysms in the setting of intracranial hemorrhage.

The next step in the ENLS prescribed algorithm is to pursue lab work. As discussed previously in this section, there are a variety of metabolic and toxic etiologies that can cause coma. Unless a readily reversible cause has been identified and reversed, such as hypoglycemia, additional laboratory testing should be obtained. Initial testing typically involves serum chemistries, basic hematological panel, blood gas analysis, ethanol level, and toxicology screen.

Further Testing

If no structural cause has been identified, and the workup described above is unclear, further diagnostic testing should include an electroencephalogram (EEG) to evaluate for nonconvulsive status epilepticus or post-ictal state, as well as any signs that may suggest particular metabolic or toxic derangements. Lab workup can be expanded to include thyroid function panel to evaluate for hypothyroidism, thyrotoxicosis, and myxedema coma; hepatic panel and ammonia testing to evaluate for hepatic encephalopathy; and acetaminophen levels and other drug levels based on history obtained. If there is no significant risk for downward herniation identified on imaging, and no clinical signs of high ICP, then a lumbar puncture should be pursued to evaluate for signs of inflammation and infection within the CNS.

Management of Cerebral Herniation

The first step is securement of the "ABCs" – airway, breathing, and circulation – using the ACLS and ATLS algorithms. However, once this is done, other emergent treatment considerations should also be pursued while the cause of the coma is still under investigation. This involves assessing for and treating cerebral herniation syndromes. This section describes the management of cerebral herniation. As the etiology of the coma becomes evident, disease-specific treatments should be implemented, and these are described in the disease-specific chapters of this textbook.

If the patient exhibits clinical evidence of intracranial hypertension (e.g., coma, pupillary abnormalities, Cushing's triad), a "brain code" should be performed. A "brain code" is the systematic administration of therapies to lower intracranial pressure.

The algorithm below summarizes the steps involved in a brain code

1. Position head of bed to at least 30°, make sure the neck is straight and that the sides of the neck are not being compressed.
2. Hyperventilate the patient to a goal PaCO2 of 28–32.
3. Review, access, and administer one of the following:
   (a) 1 g/kg mannitol [can be given through a peripheral IV, IO, or central line]
   (b) 23.4% Hypertonic saline push (colloquially known as a saline bullet) [can be given through an IO or central line]

4. If unsuccessful with either of the above, administer the other therapy.
5. If still unsuccessful, start hypertonic saline with a bolus and then infusion.
6. Consider placement of an intraventricular catheter – extraventricular drain system (IVC or EVD). This requires a noncontrast head CT to guide placement.

When cerebral herniation is first identified at the bedside, usually in the form of a dilated pupil, the most rapid intervention is to ensure that venous drainage is not being impaired through positioning. This involves setting the head of the patient's bed up at an angle greater than 30° and making sure the jugular veins are not being compressed by external devices.

Next, hyperventilate the patient with a goal PaCO2 of 28–32. If the patient is intubated and on mechanical ventilation, this can be accomplished by increasing the set respiratory rate up to approximately 25–30 breaths per minute. If the patient is not on mechanical ventilation, the same effect can be achieved through adequate bag mask ventilation. End-tidal carbon dioxide monitors should be used where possible to guide hyperventilation therapy. Hyperventilation works by inducing cerebral vasoconstriction, thereby decreasing the amount of blood in the intracranial compartment and creating more space and alleviating the downward cerebral herniation.

The next step in treatment is to administer an agent that would pull fluid out of the cerebral interstitial fluid and tissue and into the blood vessels, so as to deliver it out of the cranium, thereby decompressing the brain. Mannitol (20% or 25%) and hypertonic saline are the agents of choice. Mannitol creates an osmotic gradient allowing water to flow out of both the edematous and normal brain, which decreases cerebral volume and, consequently, intracranial pressure. Mannitol can be easily administered through a peripheral intravenous line. Hypertonic saline comes in different concentrations. A 23.4% hypertonic saline push, colloquially known as a "saline bullet" is preferred in the emergent herniation setting. Historically, it required the placement of a central venous catheter to administer, but recent evidence has shown that it can be safely administered using an intraosseous line, which can be placed quickly in emergency settings [41]. No matter which you start with, mannitol or hypertonic saline, if you are unsuccessful in restoring pupillary reactivity, administer the other agent as well. 2% saline can be administered safely through a peripheral intravenous line, and 3% saline use through peripheral intravenous lines tends to be institution specific based on available nursing safety protocols.

Finally, if these medical interventions are unsuccessful, CSF diversion out of the cranium using an IVC/EVD may be a possible solution. This does however require at least a recent noncontrast head CT to help the proceduralist plan and place the device.

While the mortality of acute intracranial hypertension is high, with frequent progression to brain death, there is significant potential for good neurological outcomes. In a prospective study of 28 patients with acute intracranial hypertension and cerebral herniation, 16 (~60%) patients died, including the 13 patients who progressed to brain death. However, with aggressive medical therapy as described in the preceding paragraphs, seven (25%) of these patients were functionally independent in approximately 1 year [42]. In a retrospective study of the efficacy of 23.4% NaCl in the reversal of cerebral herniation, 5 of 68 patients (7.4%) had mild or moderate disability at discharge [43]. Both of these studies indicate that despite the high risk of severe disability and death due to intracranial hypertension and cerebral edema, prompt recognition and initiation of a "brain code" can lead to good neurological outcomes in up to 25% of affected patients.

Complete Neurological Assessment of the Comatose Patient

The purpose of a complete neurological examination in comatose patients is to localize the lesion responsible for failure of arousal. This more comprehensive evaluation should be performed after emergent assessment and stabiliza-

tion of an acutely comatose patient. Neurological examination and anatomical localization allow for an accurate assessment of the condition of the patient as an important guide for immediate and future investigation and therapy. The neurological examination in the comatose patient is performed with the same format as in conscious patients, except that the approach is modified for performance in a patient who cannot cooperate or follow commands [44]. The standard format of the general neurological examination proceeds through each of the following neurological systems: mental status and/or level of consciousness; cranial nerves; motor system; sensory system; reflexes; coordination; and gait. In a poorly arousable patient, assessment of the level of consciousness is paramount and takes precedence over the standard mental status examination, in which the content of consciousness is assessed. In fact, further assessment of the content of consciousness (e.g., language, calculation, memory) is not possible or reliable without an adequate level of arousal. Cranial nerves, motor and sensory systems, and reflexes are also examined in detail. Examination of coordination and gait is more difficult in an uncooperative patient and does not usually contribute to neuroanatomical localization in disorders of arousal.

In disorders of arousal, accurate assessment of the level of consciousness is imperative. The approach to examination of a patient's level of consciousness is to ascertain the degree of wakefulness, orientation, and attention. The first step in examining an unresponsive patient (after the rapid neurological assessment) is to observe the patient for a period of time to assess whether the patient arouses spontaneously (to internal stimuli). The next step is to assess the patient's responsiveness to external (examiner-induced) stimuli. These stimuli should be applied in a graded fashion from least to most noxious. Common stimuli include the following: voice or loud sound, especially calling of the patient's name; painful stimulus (pinch or rub) applied to arm, leg, trapezius muscle, chest, or orbit; nasopharyngeal stimulation with a cotton swab; and in-line suctioning of endotracheal or tracheostomy tube. Attention should be paid to the amount of stimulation needed for arousal, the level of arousal achieved with stimulation, and how long the patient remains aroused after discontinuation of the stimulus. If the patient arouses reliably, then the level of attention and orientation can be assessed by performing a limited mental status exam or a Folstein Mini-Mental Status Exam (MMSE). The patient should be asked to follow commands or verbalize if not intubated. If verbal, the patient should be asked to state his name, the location, the date or year, season, and reason for hospitalization. Cues can be given, but the use of cues should be accounted for when assessing level of arousal, i.e., reliance on cues suggests less orientation and more abnormal arousal. Patients should also be asked to follow commands. Midline commands (e.g., eye opening and closing, sticking out the tongue) should be tested first, followed by appendicular commands (e.g., showing two fingers or thumbs up). An ability to follow appendicular commands belies more complex processing and higher level of arousal than obeying midline commands alone. A patient in coma will not follow commands, open eyes, arouse to any painful or noxious stimuli, or respond in any meaningful way. An encephalopathic patient will arouse, open eyes, and follow commands inconsistently.

The cranial nerve examination is important for localization of the lesion responsible for the altered level of consciousness and to monitor for disease progression. The RAS, which controls cortical activation and arousal, traverses the brainstem longitudinally and is anatomically proximate to many cranial nerves and their nuclei, especially those from the mid-pons and more rostrally. Examination of the cranial nerves proceeds in the numerical order of the nerves, with exclusion of the olfactory nerve (first cranial nerve). The function of the optic nerve (second cranial nerve) can be examined through several approaches. In an unresponsive patient, the integrity of optic nerve function is examined by testing for pupillary function, blink reflex to a threat stimulus, and the ability to track visual stimuli. When testing pupils, light from the examiner is directed onto the retina, and pupil constriction (miosis) is triggered. Miosis requires an intact

optic nerve, midbrain, oculomotor nerve (third cranial nerve), and parasympathetic nervous system. Furthermore, in normal patients, when light is directed into one eye, both pupils constrict consensually. Pupillary constriction and the consensual response in the contralateral eye are dependent on the Edinger–Westphal nucleus, which is located in the midbrain. To activate this pathway, an examiner's light stimulates retinal ganglion cells located in the retina. Most of the retinal ganglion cells project via the optic nerves and tracts to the lateral geniculate nucleus and ultimately the visual cortex to encode visual information. However, a number of neurons project to the pretectal nucleus of the midbrain and thus form the afferent limb of the pupillary light reflex. From the pretectal nucleus, the pathway projects to the Edinger–Westphal nucleus, which gives rise to the pupil-constricting fibers of the oculomotor nerve. A lesion along these pathways could cause an inability of one or both pupils to constrict, depending on the precise location of the lesion and the structures affected. A lesion involving the optic nerve will lead to an inability of both pupils to constrict consensually to light directed into the affected eye because the afferent limb of the pupillary light reflex is dysfunctional. This type of lesion can be highlighted using the swinging flashlight test, where the examiner's light is directed into each eye alternately. During this test, when the light is directed into the affected eye, both pupils dilate. In contrast, when the light is directed into the normal eye, both pupils constrict appropriately. Lesions affecting the optic nerve in isolation rarely affect the level of consciousness. The most common location for lesions affecting both the pupillary light reflex and the level of consciousness is in or near the midbrain, and such lesions usually result in oculomotor nerve or nucleus dysfunction. Examination of oculomotor nerve function will be discussed below.

A test for reflexive blink to visual threat is another way to test the optic nerve in an unresponsive patient. The examiner can move his fingers or hand toward the patient's eye in a brisk, "threatening" manner and can even present the stimulus within quadrants of confrontational visual field testing. Reflexive blink to a visual threat requires an intact optic nerve, which serves as the afferent limb of the reflex pathway, and an intact facial nerve, which serves as the efferent limb of the pathway producing a blink response. However, an absent reflexive blink to visual threat is nonlocalizing because lesions producing a failure to blink to threat have been postulated in multiple disparate locations, including the striate cortex, higher-order visual processing centers, frontal eye fields, and mid- to upper brainstem [45]. Reflexive visual stimulus tracking can also be examined in an unresponsive patient. Like the blink-to-threat pathway, tracking of visual stimuli is also controlled through a complex neurological pathway. Nonetheless, the afferent limb is also the optic nerve. To test for the ability to track visual stimuli, various items and objects can be moved through the visual fields. Most directly, the patient can be asked to follow fingers or a face with his eyes. Several powerful stimuli to test the ability to track are the human face, paper money, and photographs of loved ones. Another tracking stimulus is the optokinetic nystagmus (OKN) strip or wheel, in which a strip of paper or wheel with alternating colors is moved across the patient's visual fields. OKN strips or wheels trigger nystagmus in normal patients. In order to have a normal response to OKN testing, patients must have intact optic nerves in addition to intact higher-order cerebral processing centers, such as in the occipital and parietal cortices [46]. OKN testing can be used to test for normal optic nerve and visual function in an unresponsive patient, but absent OKN is difficult to localize.

The oculomotor nerve (third cranial nerve) has two principal functions (1) control of pupillary constrictors and (2) extraocular eye movements. Again, bilateral symmetrical pupillary constriction requires intact optic nerves (second cranial nerve), midbrain, oculomotor nerves (third cranial nerve), and parasympathetic nervous system function. The efferent limb of the pupillary light reflex begins at the Edinger–Westphal nucleus, which gives rise to parasympathetic fibers that travel within the medial aspect of the midbrain before joining onto the surface of the oculomotor nerve. The nuclei of the oculomotor nerve also

are located in the medial aspect of the midbrain and give rise to the fibers that control eye movements. The eye movements controlled by the oculomotor nerve include all of the cardinal directions (upward, downward, medially) in the ipsilateral eye, except lateral and the combination of downward and medial. The lateral and downward/medial movements are controlled by the lateral rectus nerve (sixth cranial nerve) and trochlear nerve (fourth cranial nerve), respectively.

Integrity of the oculomotor nerve and its nuclei is tested by testing pupillary function and eye movements. In the case of the oculomotor nerve, derangement of the parasympathetic fibers causes marked pupillary dilation ("blown pupil"). Damage to Edinger–Westphal and oculomotor nuclei within the midbrain causes bilateral failure of pupillary constriction and pupils that are midsized (2–4 mm) and unreactive. In contrast, damage to the pons can lead to pupils that are pinpoint and poorly reactive, due to interruption of descending sympathetic pathways and consequently unopposed parasympathetic activity produced by the midbrain. Because of the close proximity of the oculomotor nerve and nuclei to the cerebral aqueduct and the RAS, lesions affecting pupil reaction often are accompanied by arousal failure. Pupil size and reactivity, in addition to other exam findings, can help identify the precise neuroanatomical location of the responsible lesion. For example, bilaterally midsized pupils and loss of consciousness would be attributable to a medial midbrain lesion. In contrast, a fixed and dilated pupil without alteration in consciousness would likely be attributable to ipsilateral oculomotor nerve compression without impingement on the midbrain. A fixed and dilated pupil with an alteration in consciousness suggests oculomotor nerve dysfunction in or near the midbrain. Small, unreactive ("pinpoint") pupils bilaterally and arousal failure are attributable to a lesion in the upper pons.

In the unresponsive patient, extraocular movements are observed for the oculomotor and abducens nerves (third and sixth cranial nerves, respectively). Trochlear nerve (fourth cranial nerve) function is difficult to test in unconscious patients. In the unresponsive patient, spontaneous eye movements and passive eye positioning should first be observed to determine any obvious weakness. Weakness with gaze in any direction might be observed in the patient's spontaneous eye movements. The patient can be asked to track a visual stimulus or a powerful tracking stimulus, which can be moved across the patient's visual fields. As described, examples of powerful tracking stimuli include a human face, high denomination paper money, or an OKN strip or drum. In an unresponsive or uncooperative patient, eye movements can be tested using the oculocephalic reflex, also sometimes referred to as testing for doll's eyes. For this test, the examiner moves the patient's head laterally from side to side and observes the patient's lateral eye movements. Normally, tonic activity bilaterally within the vestibular systems drives the eyes to the contralateral side. This activity is balanced unless the head is moved. When the head is moved laterally, activity increases in the vestibular system ipsilateral to the direction of head movement and decreases in the vestibular system contralateral to the head movement. *Thus, in a patient with normal eye movements, the eyes move in the opposite direction to the head turn*. This test can also be performed using vertical head movements. A normal oculocephalic reflex requires a normal vestibular apparatus, vestibulocochlear nerve (afferent limb, eighth cranial nerve), brainstem, oculomotor nerve (efferent limb, medial eye movement), and abducens nerve (efferent limb, lateral eye movement). An absence of eye movements with oculocephalic testing can be due to diffusely abnormal brainstem activity or no brain activity at all. However, this test should be interpreted with caution because conscious patients can suppress the oculocephalic reflex with gaze fixation on a distant object. If the oculocephalic reflex is present in some directions but not others, then the test should be interpreted to determine which particular extraocular muscles are weak and ultimately which nerves or their nuclei have failed: the oculomotor nerves control medial eye movements, and the abducens nerves control lateral eye movements.

If the oculocephalic reflex is absent, then a stronger test to confirm absent eye movements is

the vestibulo-ocular reflex or cold caloric test. For this test, water that has been cooled for 5 min with ice is instilled continuously into one external auditory meatus for 2 min. The eyes are observed for movement during and several minutes after the infusion. After several minutes to allow rewarming, cold water should be infused into the contralateral ear. Like the oculocephalic reflex, a normal cold caloric response requires a normal vestibular apparatus, vestibulocochlear nerve (afferent limb, eighth cranial nerve), brainstem, oculomotor nerve (efferent limb, medial eye movement), and abducens nerve (efferent limb, lateral eye movement). As mentioned, normally tonic activity bilaterally within the vestibular system drives the eyes to the contralateral side. Cooling of the tympanic membrane disrupts this balance. *Thus, in a patient with normal pons and midbrain activity, inhibition of tonic activity by tympanic membrane cooling causes the eyes to move toward the cooled ear*. The lateral and medial eye movements are mediated by the abducens and oculomotor nerves, respectively. If the patient also has intact cortical activity, a corrective saccade away from the cooled ear will also be present. The classic mnemonic "COWS: *c*old *o*pposite, *w*arm *s*ame" refers to the corrective saccade produced by the different water temperatures used in caloric testing. This mnemonic has little clinical utility in the comatose patient because cortical activity is usually absent or markedly abnormal. In patients where the cold caloric response is asymmetrical or absent on one side, the other clinical and neurological examination data should be interpreted to determine the location of the lesion. In a patient with absent pons and midbrain activity, the eyes will remain in the midline during cold caloric testing on both sides. Eye motion abnormalities often accompany loss of consciousness because of the close proximity of extraocular movement nuclei to the RAS, especially in the midbrain.

Brain injury that produces arousal failure can often produce certain patterns of eye movements, which can aid in localization. Ocular bobbing is produced by pontine lesions and is defined by a rapid downbeat and slow upward phase. Midbrain lesions can produce retraction nystagmus, convergence nystagmus, and sunsetting eyes with forced downgaze. Ping pong eyes and periodic alternating gaze are induced by injuries to both hemispheres, cerebellar vermis, or the midbrain. Though rare, when present with coma or encephalopathy, these eye movement abnormalities can portend neurological catastrophe.

In the unresponsive patient, the corneal reflex is the most reliable way to test the trigeminal nerve (fifth cranial nerve) function. In this test, the cornea is stimulated, which causes a blink reflex in both eyes. This reflex requires a normal ipsilateral trigeminal nerve, pons, and bilateral facial nerves. Like the pupillary light response, there is a consensual blink response to corneal stimulation. A component of the corneal reflex is also controlled by the contralateral parietal lobe. The trigeminal nerve is the afferent limb of this reflex and can be stimulated using techniques of graded intensity. The most benign form of stimulation is to gently touch or move the patient's eyelashes. If the patient blinks symmetrically, then the corneal reflex is intact and no further corneal stimulation is needed. Corneal stimulation techniques of greater intensity include placing drops of normal saline in the eye and touching a tapered cotton swab to the cornea. The cotton swab provides the highest level of corneal stimulation. Care should be taken with repeated corneal reflex testing to avoid the region directly in the front of the lens because a corneal abrasion in this location could affect vision. It is advisable to test the corneal reflex as distal from the lens as possible, such as where the sclera and the cornea intersect.

The facial nerve (seventh cranial nerve) can be tested by observing passive face posture, such as palpebral fissure width and the nasolabial fold. As mentioned above, the efferent limbs of the blink and corneal reflexes are controlled by the facial nerve. Facial weakness should be interpreted in conjunction with other clinical variables as it relates to an altered level of consciousness. The vestibulocochlear nerve (eighth cranial nerve) is tested as described above, using the oculocephalic and vestibulo-ocular reflexes. The glossopharyngeal and vagus nerves (ninth and tenth cranial nerves, respectively) are tested via

gag and cough. Patients with a severely diminished level of consciousness often have weaker or more poorly coordinated gag and cough. The exact etiology of this poor coordination is not clear as the glossopharyngeal and vagal nuclei are often spared by lesions that affect the level of consciousness. Comatose patients are usually intubated for airway protection because even with a present gag and cough, there is a high risk of poor ventilation, aspiration, and pneumonia. The spinal accessory nerve and hypoglossal nerves are not commonly tested in the unresponsive patient.

The brainstem is responsible for control of the pattern of breathing. Lesions within the brainstem can cause pathologic breathing patterns that are typified by the location of the lesion. Cheyne–Stokes breathing is defined by short periods of hyperpnea followed by short periods of apnea and may be associated with other signs of heightened arousal, such as improved motor exam or eye opening. Cheyne–Stokes breathing usually results from bilateral thalamic injury, injury to widespread bilateral cortical projections, or metabolic derangements and is therefore frequently associated with arousal failure. Apneustic breathing is associated with pontine injury and is characterized by long inspiratory pauses. Central neurogenic hyperventilation is characterized by sustained hyperventilation with respiratory rates >40 breaths per minute. This pattern localizes injuries to both cerebral hemispheres, the pons, or the midbrain. Cluster breathing is defined by irregular clusters of breaths, followed by pauses of irregular duration. Injuries to both hemispheres, the pons, or rostral medulla can result in cluster breathing. Ataxic breathing results from medullary lesions, is defined by a completely irregular pattern (the "atrial fibrillation" of respiratory patterns), and can signal impending respiratory failure.

As in the examination of the cranial nerves, the motor system is examined first by passive observation. The examiner should note whether the patient is moving symmetrically, briskly, and spontaneously and whether the patient is posturing any extremities. Next the examiner should ask the patient to follow commands in the midline and with all four of his extremities. If the patient is conscious, confrontational power testing can be performed as in the classic neurological examination. Similarly, if the patient is awake and lucid, the sensory system can be tested in detail. However, in the unresponsive patient, the motor and sensory systems are tested together as the patient responds to painful stimuli delivered centrally and peripherally. When a painful stimulus is applied, if the patient moves any extremities or grimaces, then there is evidence that a sensory signal is being processed. If the patient moves his extremity in a complex way in response to a painful stimulus, especially against gravity, then the patient has localized. Localization is not stereotyped: the patient may perform a different or very purposeful action with each painful stimulus, which belies higher cortical processing. In contrast, withdrawal of the extremity to a painful stimulus can be stereotyped and is often within the plane of gravity. Posturing of the extremities or absent extremity movement portends severe neurologic injury. There are two types of posturing: extensor (decerebrate) and flexor (decorticate) posturing. Extensor posturing is associated with poorer clinical outcomes and usually results from injuries to larger brain territories, including the pons and midbrain. With extensor posturing, painful stimuli trigger a very stereotyped response in which the patient extends and pronates one or both arms to his side, extends both wrists, extends both legs, and plantar flexes the feet. In contrast, with flexor posturing, painful stimuli also trigger a stereotyped response except that the arms flex at the wrist and elbow. Flexor posturing is also associated with poor neurological outcomes but is caused by injury to less brain territory than extensor posturing, usually involving the regions rostral to the upper midbrain. Because of the uncertainly regarding the precise localization of these posturing reflexes, it is advised to use the terms extensor and flexor instead of decerebrate or decorticate posturing. To determine with certainty whether the patient's movement is a withdrawal or posture, the patient's hand should be placed on his abdomen and a painful stimulus

applied to the upper arm. With localization or withdrawal, the patient will move the arm away from the painful stimulus. With a posture, the arm will move in a stereotyped manner irrespective of the stimulus location. Applying a painful stimulus to the lower extremities may also trigger a triple flexion response, in which the hip and knee flex and the ankle dorsiflexes. This finding is a spinal cord reflex and is consistent with severe neurological dysfunction. While flexor and extensor posturing are associated with poor neurological outcomes, both require brain activity. The triple flexion reflex may persist in the absence of brain activity and in the setting of brain death.

Tendon reflexes play a diminished role in the examination of the comatose patient, as compared to the traditional neurological examination. The jaw jerk reflex is a reflex that tests the integrity of the trigeminal nerve and its nuclei. Elevated jaw jerk reflexes can be seen with lesions above the trigeminal nuclei and with diffuse metabolic and toxic processes that can cause altered level of consciousness. Other tendon reflexes can be tested for hyper- or hyporeactivity, which can be seen in the setting of toxic and metabolic derangements, or asymmetry which could help localize the neurological injury in conjunction with other clinical data and the neurological examination as described in the preceding sections.

Prognostication in Chronic Disorders of Consciousness

For patients that persist in a state of disordered consciousness after the acute period, the goal of management shifts toward optimizing treatment and assisting with prognostication. This is an imperfect and uncertain arena, prone to error, and for which research and novel diagnostics continue to provide new information. Furthermore, the underlying cause of injury, whether or not it is active or resolved, the patient's comorbidities, and other confounding factors make it highly difficult to prognosticate in broad groups. Individual prognostication requires expert clinical judgement, a thorough and up-to-date understanding of the current literature, and an ability to apply the relevant literature to the patient at hand. Most of the statistics in the prognosis of disorders of consciousness comes from studies looking at patients with either traumatic brain injury or anoxic-ischemic injury, typically in the setting of a cardiac arrest. Clinicians must be exceptionally careful when trying to apply these statistics to patients with other mechanisms of injury. Clinicians are also cautioned on the limitations and the low quality of the current neurologic prognostication studies for comatose survivors of cardiac arrest [47], especially in the era of targeted temperature management where neurologic findings and drug metabolism are significantly altered.

As alluded earlier in this chapter, emerging evidence suggests that covert consciousness may be present in 15–20% of patients with disorders of consciousness and these patients have a better functional recovery 1 year post-injury. Detection of these patients is currently done through fMRI and task-based EEG studies, and the use of these technologies is not widespread at this time. The JFK Coma Recovery Scale – Revised (CRS-R) is the most widely used behavioral assessment tool for detecting consciousness in subacute and chronic disorders of consciousness [48]. The current literature suggests multiple CRS-R examinations can optimize the detection of volitional behaviors. Ongoing longitudinal research using the CRS-R is attempting to characterize the long-term outcomes of patients in different disorders of consciousness.

Our recommendation for clinicians attempting to prognosticate recovery for patients with disorders of consciousness is to evaluate the specific up-to-date literature for their patients based on the specific etiology of the state, the syndrome seen at bedside, and the timepoint from injury. We discourage the extrapolation of findings to other populations that were not identical to the ones specifically studied. Further useful information from a variety of tests such as MRI imaging, EEG activity, and if possible task-based functional diagnostic studies can help assist the clinician in formulating a reasonable prognosis.

Treatment of Chronic Disorders of Consciousness

The management of patients with disorders of consciousness secondary to catastrophic brain injuries remains a challenging issue particularly in regard to the limited therapeutic options currently available. Different treatments, pharmacological and non-pharmacological, have been investigated for patients with disorders of consciousness including coma (where there is no wakefulness, reflex behaviors only), unresponsive wakefulness syndrome (UWS, previously known as vegetative state, where there is wakefulness but reflex behaviors only), and minimally conscious state (MCS, where there is clinical demonstration of signs of consciousness). Promisingly, new clinical and neuroimaging data have suggested a potential benefit of treatment for prolonged disorder of consciousness even years after the brain injury. However, despite the multitude of treatments tested, only few have been proven of limited efficacy in improving arousal. Extensive reviews of available treatment have been published elsewhere.

Pharmacological Intervention

Various drugs including amantadine (dopamine agonist and NMDA antagonist) [49–54], apomorphine (a nonselective dopamine agonist with a high affinity for D2 receptors) [55–57], intrathecal baclofen (GABA agonist) [58], zolpidem (non-benzodiazepine GABA agonist) [55, 59–63], midazolam (benzodiazepine GABA agonist), and ziconotide (calcium channel blocker) and most recently psychedelics [64, 65] have been used to improve consciousness and functional recovery in patients with disorders of consciousness.

Neurostimulants, like amantadine, are provided to enhance neural transmission by increasing the synaptic concentration of dopamine, serotonin, and noradrenaline in various brain regions. The effects of neurostimulants include enhanced arousal, wakefulness, awareness, attention, memory, mental processing speed, and/or motor processing speed. In a large class II randomized controlled trial, amantadine (up to 200 mg twice a day) accelerated the pace of functional recovery during active treatment in 184 patients with disorders of consciousness secondary to traumatic brain injury (TBI) [51]. Based on these findings, the American Practice Guidelines for patients with disorder of consciousness published in 2018 only recommends amantadine for patients with UWS and MCS between 4 and 16 weeks after a TBI [50]. Few case reports have also reported clinical improvement with amantadine in patients with disorder of consciousness secondary to causes other than TBI. The administration of one or more neurostimulants (i.e., amantadine, bromocriptine, levodopa, methylphenidate, and modafinil) has also been evaluated in a retrospective cohort study of patients with disorders of consciousness of various etiologies; however, it did not result in a meaningful improvement.

Zolpidem has been shown to modulate the thalamocortical connectivity through the disinhibition of the thalamus by acting on the globus pallidus interna and, consequently, promotes the recovery of consciousness. Zolpidem demonstrated improvement of consciousness and functional recovery in around 5% of patients [55, 59–63].

Non-pharmacological Intervention

- Invasive brain stimulation (i.e., deep brain stimulation or vagal nerve stimulation)
- Noninvasive brain stimulation [i.e., transcranial direct current stimulation (TDCS), repeated transcranial magnetic stimulation, transcutaneous auricular vagal nerve stimulation, and low-intensity focused ultrasound pulse]
- Sensory stimulation programs

Of the noninvasive techniques, TDCS has shown the most promising results. TDCS is a neuromodulation technique that can modulate cortical excitability through the application of a weak (usually $\leq$2 mA) direct current through the brain between two electrodes. It has been suggested that the underlying mechanisms by which TDCS can influence cortical activity and act on neuroplasticity depend on membrane potential

changes as well as modulations of NMDA receptor efficacy.

TDCS applied over the dorsolateral prefrontal cortex induced some clinical improvement in five randomized controlled trials (four class III and one class II evidence) in patients in MCS from TBI and non-TBI etiologies [66].

Sensory stimulation programs include, among others, motor-based therapy, auditory-based training, music therapy, and multisensory training programs. Only one double-blind randomized controlled trial has been done on sensory stimulations, showing that auditory stimulations could speed up recovery in patients with prolonged disorders of consciousness [67].

In conclusion, several randomized controlled trials have been done, but only two of them support amantadine as a pharmacological treatment and transcranial direct current stimulation as non-pharmacological treatment with class II evidence of clinical improvement in patients with chronic disorder of consciousness. Large double-blind randomized controlled trials are still needed to confirm possible therapeutic effects of other interventions, particularly to better define the phenotype of potential good candidates to these treatments and to identify a set of biomarkers that correlate with treatment response.

Brain Death

Clinical Determination of Brain Death/Death by Neurological Criteria

The advancement of cardiopulmonary resuscitation techniques has extended "life," and the concept of brain death has emerged – where there is cessation of all brain functions within an artificially maintained cardiorespiratory physiology. Catastrophic brain injuries lead to irreversible compromise of neurological function and consequent brain death. The idea of brain death was first recognized in 1959 as "coma dépassé" and subsequently clinically defined as "brain death" in 1968 by the Harvard Brain Death Criteria [68, 69]. The Uniform Determination of Death Act in 1981 legally established brain death in the United States as "irreversible cessation of all functions of the entire brain, including the brain stem [70]."

Determination of brain death by establishing cessation of neurologic function should be consistent and uniform. In 1995, the American Academy of Neurology Practice Parameter (AANPP) published guidelines on how to determine brain death in the adult patients. These guidelines were subsequently revised in 2010 in order to improve adherence [71]. The brain death standards for adults and children that are widely accepted by the medical profession are the following guidelines, the American Academy of Neurology (AAN)'s 2010 Evidence-Based Guideline Update: Determining Brain Death in Adults and the 2011 Guidelines for the Determination of Brain Death in Infants and Children, published by the Pediatric Section of the Society of Critical Care Medicine, the Sections of Neurology and Critical Care of the American Academy of Pediatrics, and the Child Neurology Society [72].

Most recently, the World Brain Death Project recently formulated a consensus declaration of recommendations on determination of brain death or death by neurological criteria (BD/DNC). These recommendations have been endorsed by international societies to improve consistency in BD/DNC determination within and between countries and to diminish confusion and variability on the worldwide acceptance of BD/DNC as synonym of human death [73–75].

Despite the efforts made in standardizing determination of BD/DNC, research continued to highlight variability in hospital policy and documentation as well as lack of training in healthcare providers when determining brain death. The lack of specificity in most states' laws, coupled with inconsistency among brain death protocols in medical facilities, has contributed to differing interpretations by the courts in a few high-profile cases [76, 77]. Improvement of medical knowledge of brain death determination and the implementation of specific uniform laws, policies, and practices across the country for the determination of brain death are critically important and have been advocated by the scientific community to provide the highest-quality patient-centered neurologic and end-of-life care. To respond to the

need for programs that train and credential physicians in the determination of brain death, the Neurocritical Care Society (NCS) recently developed a brain death toolkit [https://www.pathlms.com/ncs-ondemand/courses/1223].

Proposed Brain Death Protocol

Absolute Prerequisites BD/DNC is characterized by the irreversible and complete absence of all brain functions (determined on neurological examination as thoroughly described in the preceding paragraphs). BD/DNC is a clinical diagnosis; because of the implications and consequences of this diagnosis, a conservative approach and criteria are recommended.

(i) It is imperative for a diagnosis of BD/DNC to be considered that such a catastrophic CNS injury is identified, and all possible confounders, metabolic and toxic causes, that may mimic BD/DNC are excluded.
(ii) Neuroimaging findings are consistent with a catastrophic brain injury.
(iii) The person should have a core temperature of ≥36 °C, as defined by esophageal, bladder, rectal, or central venous or arterial catheter temperature measurements that can be achieved with available warming devices as needed.
(iv) Adults should have a systolic blood pressure of at least 100 mm Hg, or a mean arterial pressure of at least 60 mm Hg, that can be achieved with use of vascular volume, vasopressors, and/or inotropes as needed.
(v) Confounders should be eliminated or corrected if possible:
    - Pharmacological paralysis
    - CNS depressant drugs
    - Severe metabolic, acid-base, and endocrine derangements that could affect the examination
(vi) No spontaneous respirations are observed.
(vii) Clinician should be cautions and allow for an adequate observation period before BD/DNC testing. A minimum of 24 h is recommended specifically for anoxic brain injury after resuscitated cardiac arrest, while no recommended observation time has been established for other etiologies.

Neurological Examination Determination of BD/DNC can be done with a clinical examination that demonstrates coma, brainstem areflexia, and apnea. The number of clinical examinations required to pronounce BD/DNC varies according to age, hospital, state, or country and generally ranges from one to three. A single examination, including apnea testing, is the minimum standard for determination of BD/DNC for adults. Of note, if two examinations are required to declare death, the time of death is the time that the second examination is completed either by neurological examination or with ancillary tests.

The neurological evaluation for determination of BD/DNC includes an assessment for coma and an evaluation for brainstem areflexia to demonstrate that:

(i) Pupils are fixed in a midsize or dilated position and are nonreactive to light.
(ii) The corneal, oculocephalic, and oculovestibular reflexes are absent.
(iii) There is no facial movement to noxious cranial stimulation (stimuli at supraorbital nerve, temporomandibular joint).
(iv) The gag reflex is absent to bilateral posterior pharyngeal stimulation.
(v) The cough reflex is absent to deep tracheal suctioning.
(vi) There is no brain-mediated motor response to noxious stimulation of the limbs (spinally mediated reflexes are permissible).

Only if all the prior points are consistent with BD/DNC it is possible to proceed with the apnea test. If any aspect of the clinical examination cannot be completed, but to the extent completed and is consistent with BD/DNC, ancillary testing is recommended.

Apnea Test The goal of the apnea test is to challenge the medullary drive of respiration. As part

of the apnea test, the patient is disconnected from the ventilator, after being preoxygenated with a following increase in serum carbon dioxide and a decrease in the central nervous system pH to levels that would normally maximally stimulate the respiratory centers in a functioning medulla. If the medullary function is absent because permanently injured, there will be no respiratory effort in response to profound hypercarbia and acidosis.

Prior to the initiation of the apnea test, the SBP should be at least 100 mm Hg or the MAP be at least 60 mm Hg in adults (and above age-appropriate targets in pediatrics); temperature should be at least 36 °C. Before disconnecting the ventilator, the person should be preoxygenated with 100% O2 for at least 10 min, and the minute ventilation should be adjusted to establish normocarbia (PaCO2 of 35–45 mm Hg [4.7–6.0 kPa]), confirmed by a pretest arterial blood gas. The use of CPAP/PEEP (continuous positive airway pressure/positive end-expiratory pressure) can help prevent de-recruitment and decrease the risk of cardiopulmonary instability. Oxygen can also be delivered via placement of a tracheal cannula.

An arterial blood gas should be drawn at 8–10 min after the initiation of the test; then the patient should be reconnected to the ventilator. The apnea test, to be positive, targets a pH less than 7.30 and PaCO2 of at least 60 mm Hg (8.0 kPa) unless a patient has preexisting hypercapnia, in which case it should be at least 20 mm Hg (2.7 kPa) above their baseline PaCO2, if known.

The apnea test should be aborted if:

- Spontaneous respirations are observed.
- Systolic blood pressure becomes lower than 100 mm Hg, or mean arterial pressure becomes lower than 60 mm Hg despite titration of fluids/inotropes/vasopressors.
- There is sustained oxygen desaturation below 85%.
- An unstable arrhythmia occurs.

When BD/DNC can be determined by the above-described neurologic examination – without ancillary tests – the time of death is the time the arterial PaCO2 reaches the target during the apnea test as reported by the laboratory.

Ancillary Testing Ancillary tests consist of blood flow studies and electrophysiologic studies, and they are meant to support the clinical diagnosis of BD/DNC. These tests are typically used when any part of the clinical examination, including the apnea test, for any reasons, cannot be completed [78]. Also, ancillary tests should be considered when there are confounding factors that remain of uncertain interpretation (i.e., observed movements likely expression of spinal reflexes). If ancillary tests are performed, the time of death is documented as the time that the ancillary test results are formally interpreted and documented by the attending physician.

Blood Flow Studies

- Digital subtraction angiography/conventional four-vessel angiography remains the reference standard of ancillary testing. Absence of contrast within the intracranial arterial vessels, where the internal carotid and vertebral arteries enter the skull base, with a patent external carotid circulation, is consistent with BD/DNC with the highest diagnostic accuracy (both sensitivity and specificity are 100%). Four-vessel angiography is invasive and requires contrast and patient transport and equipment and operator dependence limit its routine use.
- Radionuclide angiography is another neuroimaging technique where absence of radiologic activity upon imaging of the intracranial vault is consistent with BD/DNC. This test can be done at bedside and does not require contrast; however, it provides limited evaluation of brainstem, is of limited availability, and has low specificity.
- Radionuclide perfusion scintigraphy imaging, of this SPECT (single-photon emission com-

puted tomography), is preferred over perfusion scintigraphy planar imaging as the latter has limited accuracy at the brainstem. These studies should illustrate absence of intracranial isotope in order to make a determination of BD/DNC.

- Transcranial Doppler (TCD) ultrasonography is as an alternative to conventional four-vessel cerebral angiography or scintigraphy. When used it is recommended that at least two examinations are performed at least 30 min apart to make a diagnosis of cerebral circulatory arrest. The examinations should be done bilaterally, anteriorly, and posteriorly to include both internal carotid arteries as well as the vertebrobasilar circulation. Biphasic oscillating flow and systolic spikes with reversal of flow in diastole are consistent with BD/DNC on TCD. Despite the advantage of being easily done at the bedside and being noninvasive, TCD is operator dependent; 10–20% of patients have no acoustic windows. TCD should not be used in pediatrics in the absence of validation studies.
- Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) should not be used to support a diagnosis of cerebral circulatory arrest at present, pending further research that could confirm their diagnostic accuracy.

Electrophysiologic Studies

- Electroencephalogram (EEG). The most recent consensus document on BD/DNC determination suggested EEG to no longer be used routinely as an ancillary test in adults, unless required by regional laws or policy or when other tests may not be reliable (craniovascular impedance has been affected by an open skull fracture, decompressive craniectomy, or an open fontanelle/sutures in infants). EEG is limited by potential confounding factors and has limited brainstem assessment and great interobserver variability. Indeed, given the limitations of EEG for evaluating brainstem function, when used as an ancillary test it should be used in conjunction with somatosensory and brainstem auditory evoked potentials. No detectable electrical activity (≥2 μV) over a 30-min period of EEG recording is considered consistent with BD/DNC.
- Somatosensory evoked potentials (SSEP). SSEP can be performed noninvasively at bedside. Bilateral absence of any electrical transmission through the brainstem and cerebrum in the setting of an intact signal in the brachial plexus and spinal cord has a limited specificity as an isolated test. SSEP be confounded by cervical spinal cord injury, isolated brainstem lesions, sedation, and hypothermia.
- Auditory and visual evoked potentials. Bilateral absence of waveforms through the brainstem to auditory and visual cortex is consistent with BD/DNC. However, as these evoked potentials are limited to the auditory and visual cortex and as these signals can be possibly confounded in cases of eighth nerve or brainstem lesions or retinal or optic nerve lesions, their utility as an isolated test is somewhat limited [79].

Specific Protocols Different protocols for those receiving therapeutic hypothermia and for those receiving extracorporeal membrane oxygenation (ECMO) have been recommended as these situations can pose specific challenges for the correct execution of the BD/DNC determination.

Therapeutic hypothermia or targeted temperature management (TTM), most commonly used after resuscitated cardiac arrest, can blunt brainstem reflexes and alter pharmacokinetics and pharmacodynamics resulting in delayed drug elimination in sedated patients. This poses a challenge when determining BD/DNC as one of the prerequisites is a core temperature of ≥36 °C. There is no standard on how long it is necessary to wait after treatment with therapeutic hypothermia before BD/DNC can be determined. Neuroimaging should be obtained after rewarming from TTM if the clinical exam appears consistent with BD/DNC to assess for severe cerebral edema and brainstem herniation. At 24 h after rewarming to a core temperature of ≥36 °C, recent administration of CNS-depressing medi-

cations should be assessed; if absent, BD/DNC testing can be initialed. If present, there are two recommended options:

(a) BD/DNC testing is *initiated*, and if the clinical exam is consistent with brain death, then ancillary tests are obtained.
(b) BD/DNC testing is *delayed* for a certain time for drug levels or drug half-lives to clear in consideration of renal/hepatic dysfunction (≥5 half-lives for all CNS-depressing medications).

ECMO is a life-support modality used in patients with refractory cardiac and/or respiratory failure.

Patients requiring ECMO and other forms of extracorporeal support are at high risk of complications leading to irreversible brain injury and BD/DNC, and in these patients BD/DNC determination becomes even more relevant given the artificial circulatory support prevents arrest of circulation. In general, the criteria for BD/DNC determination in patients receiving ECMO are not different from those not on ECMO, and all patients receiving ECMO should meet the absolute prerequisite, undergo the clinical exam and the apnea test, and should have the same apnea testing targets and indications for ancillary tests as previously described. However, veno-arterial ECMO is particularly problematic in this regard because it provides both gas exchange and circulatory support. CO2 elimination by ECMO prevents hypercapnia, which is required to perform an apnea test. Previous literature has shown great variability and inconsistency in determining BD/DNC in patients on ECMO.

The World Brain Death Project Consensus statement has recently provided recommendations on BD/DNC determination in patients receiving veno-arterial ECMO for circulatory and respiratory support. These recommendations are relative to certain specific aspects of BD/DNC determination that in patients receiving ECMO support are specifically challenging and are summarized below.

Recommendations on BD/DNC determination in V-A ECMO:

- The extracorporeal blood flow is maintained at all times during the BD/DNC determination in order to prevent hemodynamic instability and provide a MAP ≥60 mm Hg in adults (veno-arterial ECMO flow rates may be increased to support the MAP).
- A period of preoxygenation before the apnea test of at least 10 min should be provided for all patients receiving ECMO by administering 100% inspired oxygen via the mechanical ventilator and increasing the O2 in the membrane lung from the ECMO machine.
- During the apnea test in patients receiving ECMO, 100% oxygen is delivered to the lungs via CPAP on the mechanical ventilator or via a resuscitation bag with a functioning PEEP valve, or as oxygen flow via a tracheal cannula. If the patient being evaluated for BD/DNC is not mechanically ventilated during ECMO to maintain oxygenation during the apnea test, 100% oxygen will be provided in the sweep gas. If oxygenation cannot be maintained, the test should be aborted, and ancillary tests should be performed.
- In cases of veno-arterial ECMO with intrinsic cardiac output, arterial blood gases should be measured simultaneously from the distal arterial line and post-oxygenator ECMO circuit. The apnea test targets for both sampling sites should be pH < 7.30 and PaCO2 of at least 60 mm Hg (20 mm Hg above the patient's baseline PaCO2 for persons with preexisting hypercapnia).
- Oxygen should be maintained in the membrane lung at 100% throughout the duration of the apnea test.
- The sweep gas flow rate can be titrated to 0.5–1.0 L/min while maintaining oxygenation.
- Spontaneous breathing should be observed while targeting traditional apnea test targets via serial blood gases keeping in mind that achieving a pH less than 7.30 and PaCO2 ≥ 60 mm Hg (20 mm Hg above the patient's baseline PaCO2 for patients with preexisting hypercapnia) may take longer than in a person without ECMO support.
- The test should be immediately terminated if spontaneous respiratory movements are observed or hemodynamic instability occurs.

- Mechanical ventilation should be restarted with the prior ECMO sweep gas flow rate when the pH reaches less than 7.30 and PaCO2 reaches 60 mm Hg (20 mm Hg above their baseline PaCO2 if there is premorbid hypercapnia).

If the apnea test cannot be safely conducted or completed, an ancillary test should always be considered.

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