Coma and Altered Mental Status

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Abstract

Coma is a neurologic state that is described as loss of wakefulness and decreased awareness of one's surroundings. It is caused by multiple etiologies and is a medical emergency that must be rapidly evaluated and treated. Treatable causes (meningitis and intracranial hypertension) and emergently required interventions (neurosurgical procedures) should be addressed after evaluation of airway, breathing, and circulation. Further investigation into etiology should be performed systematically, taking into account age, history and physical exam findings. Thorough neurologic examination, laboratory evaluation and imaging can help derive the etiology of coma. Patients may fully recover, remain in a minimally conscious state or persistent vegetative state, or progress to brain death. Recovery is dependent on the underlying coma etiology. Prognostication of outcome can be performed using multimodal neurologic monitoring modalities including repeated neurologic examination, evoked potentials, electroencephalography, neuroimaging, and natural history of disease. Clinician experience, prognostics data, and familial values together can impact the long term outcomes of the patients.

Keywords

Coma • Herniation • Hypoxic ischemia • Traumatic brain injury prognosis • Vegetative state • Neurologic examination

Introduction

Coma is a neurologic state that can result from a wide variety of etiologies including both primary neurologic and systemic conditions. Evaluation of the comatose child starts with immediate assessment of airway, breathing, and circulation. History and physical examination should be rapid and thorough. Diagnosis and treatment should be tiered to initially target life threatening etiologies that are reversible and treatable. Determination of the etiology of the underlying cause will direct management. In this chapter we will (1) define coma and other states of altered consciousness, (2) review the pathophysiology underlying coma, (3) discuss the differential diagnosis of coma, (4) outline an approach to the evaluation and management of the comatose child, (5) review specifics of herniation syndromes and management, and (6) discuss prognosis.

Epidemiology

The incidence of non-traumatic coma is 30/100,000 children per year [1] and the incidence of traumatic coma in children is 140/100,000 [2], with the most severe cases comprising 5.6/100,000 [3]. Non-traumatic coma is more common in

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younger children and has a 46 % 12 month mortality rate [1]. Mortality is highly dependent on the etiology for coma, and ranges from 3 % to 84 %. Traumatic brain injury is often responsible for coma. Approximately 27 % of patients with traumatic brain injury had an initial Glasgow Coma Score of less than nine [3].

Consciousness and Coma and Altered Mental Status Definitions

Normal consciousness is a state of wakefulness and awareness of self and surroundings. *Coma* is a state of altered consciousness, with loss of both wakefulness (arousal, vigilance) and awareness of the self and environment. Coma is characterized by closed eyes and inability to be aroused to respond appropriately to stimuli [4]. Sleep-wake cycles are absent. Coma is a temporary state and evolves towards normal consciousness, a minimally conscious state, a vegetative state, or brain death.

Between normal consciousness and coma is a spectrum of states of decreasing consciousness. Decreased consciousness states are lethargy, obtundation, and stupor. *Lethargy* is a state of reduced wakefulness where subjects are sleepy but can be easily roused. *Obtundation* is characterized by sleepiness that persists even with stimulation. *Stupor* is a state of unresponsiveness with little or no spontaneous movement. Stupor resembles deep sleep, but differs from coma because vigorous stimulation induces temporary arousal. *Delirium* is an acute state characterized by decreased awareness of the environment, with changes in level of consciousness, impaired attention, and a waxing and waning course.

If a patient does not improve from coma toward a normal state, they may evolve into a vegetative state or minimally conscious state. A patient in the *persistent vegetative state* is awake but unaware and has sleep-wake cycles, but has no detectable cerebral cortical function. The eyes may be open, but there is no visual fixation or pursuit. Generally this state is not diagnosed until 1 month after the coma onset. A patient in a *minimally conscious state* has severely altered consciousness with minimal, but definite evidence of self or environmental awareness, such as following simple commands or making simple non-reflexive gestures. Recent use of functional neuroimaging has initiated controversy as to whether patients who are presumed to be in a persistent vegetative state based on clinical exam may actually be in a minimally conscious state [5]. *Akinetic mutism* is a condition of extreme slowing or absence of bodily movement with loss of speech. Wakefulness and awareness are preserved but cognition is slowed. This is caused by extensive injury to the bilateral inferior frontal lobes, paramedian mesencephalic reticular formation, or the posterior diencephalon. The *locked-in syndrome* is a state of preserved consciousness and cognition with complete paralysis of the voluntary motor system. Cortical function is intact and electroencephalogram (EEG) patterns are normal. Vertical eye movements may be preserved, allowing for some communication. The locked-in state may result from lesions of the corticospinal and corticobulbar pathways at or below the pons, posterior circulation infarcts, or severe peripheral nervous system disease such as Guillain-Barre syndrome, botulism, and critical illness polyneuropathy. Finally, coma must also be distinguished from brain death. The determination of brain death (irreversible cessation of neurologic function) is based on the absence of neurologic function with a known etiology, including absence of all brain activity, including brainstem function [6]. The diagnosis of brain death is discussed in detail in another chapter of this textbook.

Anatomy of the Brain in Relation to Coma

The reticular activating system constitutes the central core of the brainstem and extends from the caudal medulla to the thalamus and the basal forebrain. The reticular activating system transmits sensory input from the periphery through the brainstem to the cerebral cortices. The reticular activating system activates the cortex, participates in feedback control and is responsible for regulating arousal. Bilateral cortical injury or brainstem injury impacting the reticular activating system connections results in coma.

Causes of Coma

The causes of coma are broad and are listed in Table 33.1. Non-traumatic coma may be due to primary brain dysfunction, such as seizures or encephalitis, or secondary impact on

Table 33.1 Causes of coma

Trauma
Parenchymal injury
Intracranial hemorrhage
Epidural hematoma
Subdural hematoma
Subarachnoid hemorrhage
Intracerebral hematoma
Diffuse axonal injury
Accidental vs non-accidental
Concussion
Non-traumatic causes
Hypoxic ischemic encephalopathy
Shock
Cardiopulomary arrest
Near drowning
Carbon monoxide poisoning
Stroke

Table 33.1 (continued)

Toxins
Medications: narcotics, sedatives, antiepileptics, antidepressants, analgesics, aspirin
Environmental toxins: organophosphates, heavy metals, cyanide, mushroom poisoning
Illicit substances: alcohol, heroine, amphetamines, cocaine
Systemic metabolic disorders
Substrate deficiencies
Hypoglycemia
Cofactors: thiamine, niacin, pyridoxine, B12
Electrolyte and acid-base imbalance: sodium, magnesium, calcium
Diabetic ketoacidosis
Thyroid/adrenal/other endocrine disorders
Uremic coma
Hepatic coma
Reye syndrome
Inborn errors of metabolism
Urea cycle disorders
Amino acidopathies
Organic acidopathies
Mitochondrial disorders
Sepsis
Infections/postinfectious/inflammatory
Meningitis and encephalitis: bacterial, viral, rickettsial, fungal
Acute demyelinating diseases
Acute disseminated encephalomyelitis (ADEM)
Multiple sclerosis
Inflammatory/autoimmune
Sarcoidosis
Sjogren's disease
Lupus cerebritis
Mass lesions
Neoplasms
Abscess, granuloma
Hydrocephalus
Paroxysmal neurologic disorders
Seizures/status epilepticus
Acute confusional migraine
Vascular
Intracranial hemorrhage – SAH/SDH/ epidural hematomas
Arterial infarcts
Venous sinus thromboses with venous infarcts
Vasculitis

the brain due to global derangements. Causes of coma may be multifactorial such as meningitis leading to an epidural empyema and elevated intracranial pressure, sinus venous thrombosis, and status epilepticus. In a population-based study, 278 of over 600,000 children between the ages of 1 month and 16 years had 345 episodes of coma [1]. Infection was the most common cause of non-traumatic coma, accounting for 38 % of cases. Intoxication, epilepsy, and complications of congenital abnormalities each accounted for 8–10 % of cases, while accidents and metabolic causes were each responsible for 6 % of cases. Incidence of non-traumatic coma also varies with age, with the highest incidence age group being less than 1 year of age. Traumatic brain injury results in an annual hospitalization rates of 129 per 100,000 of adolescents and 80 per 100,000 for children younger than years of age [7]. Major causes of traumatic brain injury requiring care in the ICU are inflicted trauma less <1 year of age (30 per 100,000 children annually) and non-inflicted trauma in toddlers (10 per 100,000 children annually). Inflicted trauma is more common than non-inflicted trauma for children under 1 year of age.

Evaluation of the Comatose Child

The evaluation of the comatose child must be performed rapidly and thoroughly to identify and manage the immediate life threatening causes of coma. Interventions to stabilize, diagnose, and then treat the comatose patient should follow a tiered approach. Initially, one must address airway, breathing, and circulation and then move on to rapidly correctable derangements. Diagnosis and management should happen concurrently. An algorithm for initial evaluation of coma is outlined in Table 33.2 and discussed below. The Pediatric Accident and Emergency Research Group of the Royal College of Paediatrics and Child Health and the British Association for Emergency Medicine have published related guidelines, including a management algorithm (www.nottingham.ac.uk/paediatric-guideline) [8].

History

A detailed history may not always be available on initial evaluation of the comatose child, but historical information must be gathered as quickly as possible, as it may be crucial in identifying the cause of coma. The history must include a detailed description of events leading to coma, with particular attention to timing of events, potential exposures, and accompanying symptoms. Preceding somnolence suggests a metabolic or toxic or infectious cause, such as toxin ingestion, liver failure, or encephalitis; sudden onset of coma without trauma suggests spontaneous intracranial hemorrhage, seizure, or cardiac arrhythmia resulting in hypoxic-ischemic encephalopathy. Previous fever with or without neck stiffness may suggest meningitis or encephalitis, but may also be a symptom of autoimmune processes such as acute disseminated encephalomyelitis or lupus cerebritis. Acute onset of headache may be due to spontaneous intracranial hemorrhage from arteriovenous malformation rupture, aneurysm rupture, or unwitnessed trauma. Chronic headache may suggest hydrocephalus, an expanding mass lesion such

Table 33.2 Initial evaluation of coma

Airway, breathing, and circulation assessment and stabilization.
Ensure adequate ventilation and oxygenation
Blood pressure management depends on considerations regarding underlying coma etiology. If hypertensive encephalopathy or intracranial hemorrhage then lower blood pressure. If perfusion dependent state such as some strokes or elevated intracranial pressure then reducing blood pressure may reduce cerebral perfusion
Draw blood for glucose, electrolytes, ammonia, arterial blood gas, liver and renal function tests, complete blood count, and toxicology screen
Neurological assessment
GCS score
Evidence of gag reflex and pupillary exam
Assess for evidence of raised intracranial pressure and herniation
Assess for abnormalities suggesting focal neurologic disease
Assess for history or signs of seizures
Administer glucose intravenously if hypoglycemic
If there is concern for infection with fever of neck rigidity and LP must be delayed broad spectrum infection coverage to treat bacterial and viral meningitis (e.g., Vancomycin/cefotaxime (ampicillin if less than 1 month to treat listeria) and acyclovir for potential HSV)
Give specific antidotes if toxic exposures are known
For opiate overdose administer naloxone
Identify and treat critical elevations in intracranial pressure
Neutral head position, elevated head by 20°, sedation
Hyperosmolar therapy with mannitol 0.5–1 g/K or hypertonic saline
Hyperventilation as temporary measure
Secure the airway
Consider intracranial monitoring
Consider neurosurgical intervention
Head CT
Treat seizures with IV anticonvulsants. Consider prophylactic anticonvulsants
Investigate source of fever and use antipyretics and/or cooling devices to reduce cerebral metabolic demands
Detailed history and examination

Consider: lumbar puncture, EEG or extended long term EEG monitoring, MRI, metabolic testing (amino acids, organic acids, acylcarnitine profile), autoimmune testing (ANA panel, antithyroid antibodies), thyroid testing (TSH, T3, T4)

as tumor, or indolent infection. Questions about possible toxic ingestions should include a survey of medications and poisons kept in the places the child has recently been.

The child's past medical history may be valuable. A history of multiple episodes of coma, developmental delay, or other prior neurologic abnormalities suggest inborn errors of metabolism, but may also indicate the presence of epilepsy with ongoing non-convulsive seizures or a post-ictal state. Toxic ingestions or inflicted childhood neurotrauma are also suggested by multiple episodes of coma. Recent weight changes or other constitutional abnormalities suggest endocrine dysfunction. Previous history of immunosuppression or HIV may suggest atypical CNS infections. A history of uncontrolled hypertension may suggest Posterior Reversible Encephalopathy Syndrome (PRES). Previously existing cardiac disease raises the possibility of dysrhythmia or cardiac failure leading to hypoxic ischemic encephalopathy. Travel history may explain exposure to infections prevalent in certain areas, such as Lyme Disease in the northeastern Unites States. Exposure to kittens in a patient with axillary or inguinal lymphadenopathy may be a clue to infection with *Bartonella henselae*, which causes cat scratch encephalopathy.

Eliciting a history of trauma, whether accidental or inflicted, is crucial. Understanding the mechanism of injury can direct further investigation. Intracranial lesions such as epidural hematomas may result in delayed loss of consciousness and require emergent intervention. Base of the skull fractures may compromise blood flow in the carotid artery or result in dissection of the artery as it enters the skull or travels in the petrous canal. In children under 2 years of age or in non-verbal children with developmental delay or intellectual disability, it is critical to have a high index of suspicion for non-accidental trauma. A broad approach to physical exam and diagnostic testing can often uncover the source of coma in these situations.

Physical Examination

The general examination should start with assessment and continuous monitoring of the vital signs. *Hyperthermia* suggests infection, autoimmune processes, heat stroke and anticholinergic ingestion. *Hypothermia* may also be due to sepsis as well as hypothyroidism, adrenal insufficiency, chronic

malnutrition, or environmental exposure. *Hypotension* may be due to sepsis, cardiac dysfunction (which may cause or be due to neurologic injury), toxic ingestion, or adrenal insufficiency, and may lead to poor cerebral perfusion thereby causing or worsening brain injury. If not quickly normalized, diffuse or watershed hypoxic-ischemic injury may occur. *Hypertension* can be a physiologic response to increased intracranial pressure that functions to maintain cerebral perfusion pressure. Hypertension with bradycardia and a change in breathing pattern (Cushing's triad) is an ominous sign of elevated intracranial pressure and suggests impending herniation. In this situation, acutely lowering blood pressure may worsen neurologic injury by reducing cerebral perfusion. However, hypertension may be caused by toxin ingestion such as cocaine, thyrotoxicosis or renal disease, and may produce hypertensive encephalopathy (posterior reversible leukoencephalopathy) in which case management focuses on reducing blood pressure. Differentiating reactive/compensatory hypertension from a hypertensive encephalopathy may be difficult. While treating hypotension is critical to maintain cerebral perfusion, treating hypertension without understanding its cause can result in secondary neurologic injury and potential systemic injury. *Tachycardia* should raise concerns of pain, seizures, toxic ingestions, sepsis, and cardiogenic shock. *Bradycardia* is concerning for a patient who may be in a pre-arrest state from hypoxia or hypotension, hypothermia, toxic ingestion, chronic malnutrition, or intracranial hypertension.

Abnormalities in respiratory rate and pattern of breathing may indicate a systemic hypermetabolic state such as fever, intrinsic lung pathology, acid-base derangement, toxin ingestion or nervous system dysfunction. Cheyne-Stokes respiration describes a rhythmic and cycling pattern of accelerating hyperpnea followed by a fall in amplitude of breathing, decelerating rate of breathing, and apnea. It is a nonspecific pattern observed with extensive bihemispheric cerebral dysfunction, diencephalic (thalamic and hypothalamic) dysfunction, or cardiac failure. Pontine or midbrain tegmental lesions may result in central neurogenic hyperventilation. Apneustic breathing is characterized by a pause at the end of inspiration, and reflects damage to respiratory centers at the mid or lower pontine levels, at or below the level of the trigeminal motor nucleus. Apneusis occurs with basilar artery occlusion (leading to pontine infarction), hypoglycemia, anoxia, or meningitis. Ataxic breathing is completely irregular in rate and tidal volume, and occurs with damage to the reticular formation of the dorsomedial medulla [4]. Kussmaul respirations are large tidal volume, deep sighing breaths that are usually in response to severe acidosis usually seen in diabetic ketoacidosis or renal failure. Often the patient's arterial partial pressure of carbon dioxide will be low in the attempts to compensate for severe systemic acidosis.

A complete general examination may yield other important findings. Meningeal signs include involuntary hip flexion with passive flexion of the neck (Brudzinski's sign) and resistance to knee extension with hips flexed (Kernig's sign). Skin examination provides information about trauma (bruises, lacerations), systemic disease (jaundice in liver failure, uremic frost, hyperpigmentation in adrenal insufficiency), and infection (superficial lacerations in cat scratch fever, erythema migrans in Lyme disease, petechiae and purpura in meningococcemia). Organomegaly raises suspicion of metabolic, hematologic, and hepatic diseases. Cardiac murmurs or a gallop, hepatomegaly, jugular venous distention, or pitting edema should raise concerns of cardiogenic shock and systemic hypoperfusion.

Neurologic Examination

While coma or altered mental status is the presenting symptom in patients, specific findings on the neurologic exam can be highly useful for determining the cause of coma as well directing further management. The neurologic examination is directed toward localizing brain dysfunction, identifying coma etiology, and determining early indicators of prognosis. As therapies are instituted for specific disease processes, continuous reassessment of the neurologic exam can help determine therapeutic impact.

Glasgow Coma Score (GCS)

Initial rapid assessment of neurologic status can be summarized in part by the Glasgow Coma Score (GCS). This score allows objective description of a patient's degree of impairment and allow the patient's state to be tracked over time and conveyed quickly to other caregivers. The GCS which was initially developed to evaluate adults with head injury [9]. Pediatric adaptations to the GCS, more developmentally appropriate for infants and children, include the Pediatric Coma Scale, the Children's Coma Scale, and the Glasgow Coma Scale-Modified for Children (Table 33.3) [10–12]. The GCS and the pediatric adaptations categorize the patient based on measures of verbal response, eye opening, and movement. Combined with other modalities, the initial GCS score may have limited prognostic value (described below). While the GCS allows efficient standardized communication of a child's state, more detailed description of the child's clinical findings is often more useful for relaying detailed information and detecting changes over time.

Response to Stimuli

Evaluation of responsiveness must include vigorous auditory and sensory stimulation inducing nail-bed pressure, pinching, and sternal rubbing. Responsiveness must be evaluated in terms of lack of verbal, motor, and cranial nerve responses.

Table 33.3 Glasgow coma scale and modification for children

Sign	Glasgow comas scale	Modification for children	Score
Eye opening	Spontaneous	Spontaneous	4
	To command	To sound	3
	To pain	To pain	2
	None	None	1
Verbal response	Oriented	Age appropriate verbalization, orients to sound, fixes and follows, social smile	5
	Confused	Cries, but consolable	4
	Disoriented – inappropriate words	Irritable, uncooperative, aware of environment – irritable, persistent cries, inconsistently consolable	3
	Incomprehensible sounds	Inconsolable crying, unaware of environment or parents, restless, agitated	2
	None	None	1
Motor response	Obeys commands	Obeys commands, spontaneous movement	6
	Localizes pain	Localizes pain	5
	Withdraws	Withdraws	4
	Abnormal flexion to pain	Abnormal flexion to pain	3
	Abnormal extension	Abnormal extension	2
	None	None	1
Best total score			15

In a comatose child, much of the examination that requires patient cooperation (such as mental status and sensory testing) cannot be performed. Thus, the exam primarily assesses function and responsiveness of the brainstem and motor systems.

A comatose child may be flaccid, or may display an abnormal posture. *Decorticate posturing* describes flexion of the arms and extension of the legs, while *decerebrate posturing* describes extension and internal rotation of the arms and legs. Traditionally, decorticate posturing has been considered to relate to dysfunction primarily in the supratentorial compartment, while decerebrate posturing has been considered to relate to brainstem dysfunction. Plum and Posner [4] describe the following guidelines to interpreting abnormal postures:

1. Flexor arm responses with or without extensor responses in the legs typically reflect less severe supratentorial damage
2. Extensor responses in the arm and leg correlate with more severe supratentorial dysfunction
3. Arm extension with leg flexion suggests pontine damage
4. Diffuse flaccidity correlates with brainstem damage below the pontomedullary level.

Cranial Nerve Examination

Examination of the cranial nerves allows investigation of both the brainstem and the cortical control of cranial nerve pathways.

Fundoscopic Examination

Fundoscopic examination evaluates the retina and optic nerves. Papilledema may be seen with increased intracranial pressure but may take hours or days to develop, so its absence does not confirm normal intracranial pressure [13]. Retinal hemorrhages may be seen in inflicted childhood neurotrauma and flame shaped hemorrhages and cotton-wool spots are seen in hypertensive encephalopathy. To obtain a reliable fundoscopic exam it is almost always necessary to dilate the pupils, which can last for up to 24 h. As will be discussed below, the pupillary exam not only contributes to the diagnosis of coma but is one of the few rapid and reliable repeated neurologic assessments. Therefore, careful thought regarding whether the pupillary exam can be forgone is needed.

Pupillary Exam

Pupillary exam should be one of the first neurologic exams performed in the comatose patient. Abnormalities in pupillary response or asymmetry in conjunction with history may require immediate life saving intervention. Asymmetric pupils are either caused by oculomotor nerve (cranial nerve III) disruption or impairment of sympathetic fibers (Horner's syndrome). Because the oculomotor nerve innervates the pupil constrictors, oculomotor nerve impairment results in an abnormally dilated pupil with an absent pupillary light reflex. Oculomotor nerve palsy also results in ptosis and ophthalmoparesis and may be a sign of uncal herniation. Horner's syndrome describes disruption of the sympathetic innervation to the face, characterized by mild ptosis over an abnormally small pupil (meiosis). In traumatic coma, Horner's syndrome may suggest dissection of the carotid artery, along which the sympathetic fibers travel, or an injury to the lower brachial plexus (C8-T1). Anisocoria (asymmetric pupils) is an important physical finding, and differentiating whether a pupil is abnormally large or abnormally small is crucial to identifying underlying pathology. When pupils are more asymmetric in bright light, the pathology lies within the

larger pupil and is likely the result of oculomotor nerve palsy. Investigations to rule out uncal herniation or an aneurysm of the posterior communicating artery should follow. As uncal herniation is a potentially treatable emergency, pupillary asymmetry and lack of pupillary reactivity require immediate assessment and treatment. Fixed and dilated pupils are concerning for herniation progressing to brain death, recent hypoxic ischemic injury, or anticholinergic administration, and thus require immediate attention.

When pupils are more asymmetric in darkness, the pathology lies with the smaller pupil. Investigation of the carotid artery, the low cervical-high thoracic spinal cord, or brachial plexus roots should follow to find causes of the Horner's syndrome. If subjects have received sympathomimetic or anticholinergic sprays or drops, it is possible that local effects have impacted one pupil leading to the asymmetry.

Eye Position and Motility

Abnormalities of eye position and motility may be signs of cortical, midbrain, or pontine dysfunction. Conjugate lateral eye deviation is caused by destructive lesions of the ipsilateral cortex or pons, or focal seizures in the contralateral hemisphere. Rarely thalamic lesions may cause "wrong-way eyes," in which the eyes deviate away from the side of the destructive lesion [14]. Tonic down gaze suggests dorsal midbrain compression.

Dysconjugate gaze suggests extraocular muscle weakness or, more commonly, abnormalities of the third, fourth, or sixth cranial nerves or nuclei. Unilateral or bilateral abducens nerve (cranial nerve VI) palsies are commonly seen in increased intracranial pressure, presumably because the nerve is stretched. An eye with an oculomotor nerve (cranial nerve III) palsy is ptotic, depressed and abducted, and has a dilated pupil. As discussed below, oculomotor nerve palsy in a comatose patient suggests uncal herniation with midbrain compression, and thus requires urgent intervention. Trochlear nerve (cranial nerve IV) palsy causes hypertropia in the affected eye.

Roving eye movements are seen in comatose patients with intact brainstem function. Their disappearance may signal the onset of brainstem dysfunction. Periodic alternating gaze (ping-pong gaze) describes conjugate horizontal eye movements back and forth with a pause at each end. It may be seen with extensive bilateral hemispheric, basal ganglia, or thalamic-midbrain damage with an intact pons, and is thought to result from disconnection of cortical influences on oculovestibular reflex generators. It has also been reported in reversible coma from monoamine oxidase and tricyclic antidepressant toxicity.

Oculocephalic and Oculovestibular Reflexes

Oculocephalic and oculovestibular reflexes are useful for assessing the integrity of the midbrain and pons in a comatose patient. To test oculocephalic reflexes ("Dolls eye" reflex), the examiner holds the patient's eyelids open and quickly moves the head to one side. In a comatose patient with an intact brainstem, the eyes will move in the direction opposite the head motion. For example, if the head is moved to the right, the eyes will move conjugately to the left. After several seconds, the eyes may return to a neutral position. The head should be tested in both horizontal and vertical directions. Oculocephalic reflexes should not be tested if the patient has sustained cervical spine trauma or if the spine has not been cleared.

The oculovestibular reflex, commonly referred to as cold calorics, tests the function above the pontomedullary junction. The child must have an open external auditory canal with an intact tympanic membrane (including the absence of pressure equalization tubes), so visual inspection of the canal is an important first step. With the head elevated at 30°, up to 120 mL of ice water is introduced in the ear canal with a small catheter. A conscious patient would experience nystagmus with slow deviation of the eyes toward the irrigated ear and a fast corrective movement away from the ear. In a comatose patient, the fast correction mediated by the cortex is not seen. Instead, the eyes will deviate slowly toward the irrigated ear and remain fixed there. If the brainstem vestibular nuclei (located at the pontomedullary junction) are impaired, no movement will be seen. In brain death, where there is no brainstem function, no eye movement is seen with both ears tested. Five minutes should be allowed before the second ear is tested to allow return of temperature equilibrium between the two ears.

Gag Reflex

The gag reflex is elicited when the soft palate is stimulated and produces elevation of the soft palate. The afferent and efferent signals are carried by the glossopharyngeal and vagus nerves respectively, with processing in the medulla. Absence of the gag reflex should be assessed during the initial airway assessment of the comatose patient. Absence of a gag reflex should raise the concern for the need for tracheal intubation for airway protection, even if the patient is spontaneously breathing with adequate oxygenation and ventilation.

Other Brainstem Reflexes

The remaining brainstem reflexes provide information about the integrity of lower regions of the brainstem. The *corneal reflex* is tested by tactile stimulation of the cornea, which should elicit bilateral eyelid closure. The afferent signal is carried by the trigeminal nerve (cranial nerve V), and the efferent pathway is carried by the facial nerve (cranial nerve VII). Completion of the reflex loop requires intact trigeminal and facial nerve nuclei in the mid and lower pons. The *cough reflex*, which may be seen with stimulation of the carina

when a patient is intubated or undergoes suctioning, is mediated by medullary cough centers; sensory and motor signals are carried by the glossopharyngeal (cranial nerve IX) and vagus (cranial nerve X) nerves. Narcotics may suppress cough reflex, an important consideration for accurate assessment of brainstem function [15].

Diagnostic Testing

Diagnostic testing should occur simultaneously with the history and physical examination. Initial blood sampling should include serum glucose, sodium, calcium and magnesium levels as hypoglycemia and electrolyte abnormalities can produce altered mental status, coma, and seizures. Hypoglycemia (capillary glucose <2.6 mmol/L) can cause direct brain injury and must be treated emergently and aggressively with intravenous dextrose. Other initial tests should include a chemistry panel to evaluate for acidosis and renal function, a hepatic function panel to evaluate for signs of elevated bilirubin or hepatitis, a complete blood count to evaluate for signs of infection, anemia or thrombocytopenia, an ammonia level for metabolic dysfunction, and a blood gas to assess for adequate ventilation and metabolic derangements. If fever is present then a blood culture should also be obtained. A lumbar puncture to evaluate for the presence of meningoencephalitis (specifically cell count, gram stain and culture, protein and glucose and herpes PCR) should be performed. However, if the patient is not stable for lumbar puncture or cerebrospinal fluid cannot be obtained, then antibiotic and/or antiviral administration should not be delayed. A serum toxicology screen to evaluate for serum levels of ethanol, tricyclic antidepressants, acetaminophen and salicylates should be performed and urine test for narcotics, benzodiazepines, cocaine, and barbiturates.

After initial laboratory assessment, other laboratory tests are based upon the clinical context and may yield information about the metabolic state of the patient. These include serum or cerebrospinal fluid lactate, pyruvate, organic acids, amino acids, and acylcarnitine profile. If the cause of coma remains unknown, additional studies may be directed at uncommon causes of coma in pediatrics such as Hashimoto's encephalitis (thyroid function tests and thyroid autoantibodies), cerebral vasculitis (ESR, ANA panel, and possibly angiography) or paraneoplastic disorders.

After initial resuscitation, a CT scan of the brain should be performed in all children to evaluate for the presence of intracranial hemorrhage, space occupying lesions (such as tumor or abscess), cerebral edema, focal hypodensities (such as acute disseminated encephalitis, herpes simplex encephalitis, infarct), or hydrocephalus. If the patient is febrile, prior to performing a lumbar puncture, a CT scan should be evaluate for intracranial hypertension, however, antibiotics should not be delayed for imaging. If there is clinical or radiological evidence for intracranial hypertension, then lumbar puncture should be deferred and treatment should be initiated for possible infections (bacterial and viral) until the clinician deems it safe to perform and lumbar puncture. Importantly, a normal CT scan does not rule out elevated intracranial pressure, sinus venous thrombosis, early ischemic stroke, hypertensive encephalopathy, or demyelinating processes. Once the patient has been stabilized and the etiology of coma remains unclear, a brain MRI may be performed for diagnostic and prognostic purposes.

An electroencephalogram (EEG) may detect useful background changes and may identify subclinical seizures. A prolonged EEG may be required to detect subclinical seizures. If there is clinical evidence of seizures then benzopdiazepines or other anticonvulsants should be administered while awaiting the EEG.

Associated Problems

Intracranial Hypertension

Depending on etiology of coma, patients may develop intracranial hypertension. The Monro- Kelli doctrine states that the skull is a fixed space with three compartments: blood, cerebral spinal fluid and brain parenchyma. Increases in one compartment will lead to a compensatory decrease in the other compartments. When there is a chronic increase in one compartment, then other compartments may gradually accommodate the increase. For example, if a tumor expands, some CSF reduction (reduced ventricle size) may occur, keeping intracranial pressure normal. However, when there is an acute change, such as an epidural hematoma or cerebral abscess, the ability of other compartments to compensate may be overwhelmed, producing an elevation in intracranial pressure. This may produce herniation which if not emergently treated can lead to brain death. Additionally, this may further compromise cerebral perfusion, resulting in further hypoxic-ischemic injury and swelling, and thus further elevations in intracranial pressure.

Numerous processes can result in elevated intracranial pressure. Hydrocephalus in an acute setting is generally the result of a blockage in cerebrospinal fluid flow, leading to its accumulation and resultant elevated intracranial pressure. Blockage can occur due to structural lesions, such as intraventricular hemorrhage or tumor or abscess blocking a usual flow path. Intracranial blood due to hemorrhage can be epidural, subdural, subarachnoid, intraparenchymal or intraventricular. Finally, cerebral edema may be vasogenic, cytotoxic

or osmolar in origin. Vasogenic edema is due to a breakdown in the blood brain barrier allowing intravascular proteins into the parenchymal space. This can be sewn following traumatic brain injury or with parenchymal tumors or abscesses. Cytotoxic edema is due to cellular derangements as a consequence of homeostatic processes to control excitotoxicity or acidosis with sodium and water accumulation leading to cellular necrosis. Osmolar edema can occur with electrolyte derangements and fluid influx to the brain such as in hyperosmolar coma.

In the event that these processes produce continuing elevation in intracranial pressure, herniation occurs. There are multiple types of herniation, but most involve compression or distortion of the reticular activating system producing worsening altered mental status, compression of the brainstem producing new cranial nerve deficits and vital sign changes, and compression of arteries further reducing cerebral perfusion. Initial management of critically elevated intracranial pressure includes evaluation of airway breathing and circulation and determining whether the airway should be secured. Initial hyperventilation should be instituted to acutely decrease cerebral blood flow. Further reduction in pCO2 may be necessary to achieve rapid but temporary reductions in cerebral blood flow and thus intracranial pressure, but excessive or prolonged hyperventilation may compromise cerebral perfusion resulting in further hypoxic ischemic brain injury. The head of the bed should be elevated to 30° to aid in venous drainage. Maintaining a neutral neck position may also improve venous drainage. Hyperosmolar therapy can be instituted to decrease cerebral edema. Mannitol will remove water from the brain parenchyma and lead to a large urinary osmotic dieresis and 3 % hypertonic saline will act as a volume expander while removing fluid from the brain parenchyma. Depending on the cause of intracranial hypertension these may only be temporizing solutions. Tracheal intubation should be considered to decrease the metabolic demand of the brain, control ventilation and oxygenation and allow for administration of medications. Barbiturate coma or hypothermia may reduce cellular energy requirements and may thus help protect the brain during periods of hypoxia and ischemia. Similarly, providing adequate sedation and paralysis may further reduce energy demand and prevent spikes in intracranial pressure. Surgical intervention for placement of a ventriculostomy is warranted it here is severe hydrocephalus. Surgical evacuation of hematomas and abscesses can reduce intracranial pressure. At times a decompressive craniectomy will allow brain contents to herniate outward, thereby reducing intracranial pressure. Herniation syndromes are summarized in Table 33.4. While neuroimaging will demonstrate the exact nature of the herniation, waiting and transport for neuroimaging may be detrimental and medical interventions should be implemented.

Table 33.4 Herniation syndromes

Herniation syndrome	Location	Signs
Central herniation	Increased pressure in both cerebral hemispheres causing downward displacement of the diencephalon through the tentorium, causing brainstem compression	**Diencephalic stage**: withdraws to noxious stimuli, increased rigidity or decorticate posturing; small reactive pupils with preserved oculocephalic and oculovestibular reflexes; yawns, sighs, or Cheyne-Stokes breathing **Midbrain-upper pons stage:** decerebrate posturing or no movement; midposition pupils which may become irregular and unreactive; abnormal or absent oculocephalic and oculovestibular reflexes; hyperventilation **Lower pons-medullary stage**: no spontaneous motor activity but lower extremities may withdraw to plantar stimulation; mid-position fixed pupils; absent oculocephalic and oculvestibular reflexes; ataxic respirations **Medullary stage**: generalized flaccidity; absence pupillary reflexes and ocular movements; slow irregular respirations, death
Uncal herniation	Uncus of the temporal lobe is displaced medially over the free edge of the tentorium	Ipsilateral third nerve palsy (ptosis, pupil fixed and dilated, eye deviated down and out) Ipsilateral hemiparesis from compression of the contralateral cerebral peduncle (Kernohan's notch) Other signs of brainstem dysfunction from ischemia secondary to compression of posterior cerebral artery
Subfalcine (Cingulate) herniation	Increased pressure in one cerebral hemisphere leads to herniation of cingulated gyrus underneath falx cerebri	Compression of anterior cerebral artery leads to paraparesis
Tonsillar herniation	Increased pressure in the posterior fossa leads to brainstem compression	Loss of consciousness from compression of reticular activating system Focal lower cranial nerve dysfunction Respiratory and cardiovascular function can be significantly affected early with relative preservation of upper brain stem function such as pupillary light reflexes and vertical eye movements

Seizures

Subclinical seizures in critically ill patients may be an under-recognized phenomenon, so the index of suspicion in a comatose child should be high. Recent studies of critically ill children demonstrate a high occurrence of subclinical seizures and status epilepticus [16–19]. Studies in adults have demonstrated that non-convulsive seizure duration and time to detection predict outcome in patients with NCSE. When NCSE was diagnosed within 30 min of onset mortality was 36 %, whereas when diagnosis was delayed for over 24 h, mortality increase to 75 %. When NCSE lasted less than 10 h, 60 % of patients returned home. However, when NCSE lasted more than 20 h none of the patients returned home and 85 % died [20].

Outcome Prediction

General Considerations

Coma is a non-specific behavioral state that can be the consequence of multiple processes, and therefore outcomes are closely related to the underlying etiology. Wong [1] reported that in 283 episodes of pediatric coma (defined as GCS <12 for at least 6 h) mortality at about 1 year ranged from 3 % to 84 % depending on etiology. Children less than a year of age were more likely to die, however, this was closely associated with etiology of coma. Accidents (smoke inhalation, strangulation, burns, drowning) and infections had higher mortality rates (60–85 %) than causes such as metabolic changes (diabetic ketoacidosis, inborn errors of metabolism), epilepsy, and intoxication (3–26 %). Morbidity, defined by severity of neurologic impairment, was more common in older children, but was not associated with specific etiology of coma.

Traumatic brain injury outcome is associated with the initial severity of brain injury. The overall US pediatric mortality for children <15 years is 11.8/100,000. Age impacts outcome, in part tied to etiology of trauma. Children <4 years old have a higher mortality than children between 5 and 9 years and 10 and 14 years (5.3 vs 2.6 vs 3.9/100,000) [21]. Younger children may have more severe long term brain injury when compared to older children [7]. Young children with non-accidental traumatic brain injury have worse outcomes than children with accidental traumatic brain injury (see the chapter on inflicted trauma later in this textbook).

Prognosticating outcome is important to help guide future management and prepare families' expectations. An overly negative prediction may lead to withdrawal of treatment in a child with a potentially salvageable quality of life. Alternatively, providing an overly positive prediction in a child who has a high probability of never regaining consciousness may lead to survival past the acute stage with return of spontaneous breathing and resultant prolonged persistent vegetative state, a condition that the child or family may not have wanted. Therefore, reliable and accurate prognostic evaluations are important to guide families' and practitioners' decision making.

Many studies provide little information regarding the exact definitions of terms such as "good" or "poor" outcome or "mild", "moderate", or "severe" neurological disability. Further, neurologic disability is not equivalent to quality of life, which depends on individual's and family's personal set of values. As Shewmon [22] described, the terms "poor/unfavorable" and "good/favorable" which are used as the outcome measures in most studies of coma prognosis are not descriptive of neuro-developmental state, but convey judgment regarding quality of life. For some, a good outcome requires the child to be fully interactive and self-sufficient, while for others a good outcome is a child who lives in any state. Furthermore, a family's perception may change over time as they live with the disabled child. Therefore, data on prognosis cannot be used in isolation to make judgments regarding quality of life, since so many factors (i.e., psychological traits related to resilience, social support) beyond neurological disability are intertwined.

Data suggests that improvement may continue for several years after injury, so determining when to measure outcome is complicated. In children with severe traumatic brain injury, the percent of children who were independent in all areas of function increased from 37 % at discharge from the hospital to 65 % at a median follow-up of 24 months [23]. While most children who are survive to discharge after a cardiac arrest are alive at 1 year, detailed long term neurologic outcomes for this survivors in a small study does not show long term neurologic improvement [24]. Many studies have evaluated prognostic tools based on hospital discharge thereby, leaving clinicians without important data regarding long term recovery. While data regarding prognosis are useful and needed, the goal may be to distinguish between a persistent vegetative state and some degree of consciousness (even with severe disability) as opposed to distinguishing between different levels of disability.

Scoring Tools

Multiple tools have been developed to repeatedly assess a patient's function and progress. These tools assess neurologic examination, daily function, and overall quality of life. The Pediatric Cerebral Performance Category (PCPC) and Pediatric Cerebral Outcome Category (POPC) are validated tools which evaluate patient neurologic outcome at ICU discharge and up to 6 months following discharge. They have been validated against more robust measures [25–27]. The

Glasgow Outcome Score is a five point scale initially used to assess outcomes for patients who have suffered traumatic brain injury [28]. These gross measures are used mainly for research purposes and can be followed over time. Tools for more granular assessment of outcome following pediatric brain injury take into account communication, daily living, social, and motor domains of adaptive behavior. The Vineland Adaptive Behavioral Score is validated from birth to 18 years of age and can be administered to a care provider [29]. The Bayley Development Score can assess outcomes in children from 0 to 3 years of age whereas other scores such as the Wee-Fim can measure disabilities in older children. Other tools can evaluate executive processing, memory and learning and may be helpful to evaluate long term functional impact. Quality of life tools can evaluate the impact of residual injury on both patients and families. Measuring these outcomes can assess the impact of injury on patients and families.

Adjunct Tools

While prognosis from coma is dependent upon etiology, certain adjunctive tools can be helpful to determine outcomes. Helpful factors include neurologic examination, neurophysiologic studies such as EEG and evoked potential testing, and neuroimaging. The reliability and validity of these tools is closely linked to patient population in which they were studied and therefore may not be generalizable to the heterogeneous comatose population.

Neurologic Exam

Specific neurologic exam findings can guide outcome prediction, especially in the acute period. While no specific early physical exam finding is 100 % predictive of outcome, certain findings in conjunction with other modalities can guide the practitioner. Following adult cardiac arrest, poor outcome is predicted by the absence of pupillary responses and absent corneal reflexes within days 1–3 after CPR, as well as absent or extensor motor responses after 3 days [30]. Several small pediatric cardiac arrest studies draw similar conclusions [31–33]. In children with coma due to multiple etiologies, the absence of motor response to pain on day three after injury had PPV for unfavorable outcome of 100 % [34].

Neurophysiology

Electrophysiological measures such as electroencephalography (EEG) and somatosensory evoked potentials may be helpful in predicting outcome early on in coma. The EEG is a good indicator of thalamocortical function, but the utility of a single EEG is limited by the lack of specificity of findings. EEG patterns may evolve over time and combined with clinical findings may help prognosticate outcome. Specific background patterns such as low amplitude, discontinuity, lack of reactivity and electrocerebral silence are associated with poor outcome in comatose children [31, 35, 36]**.** The sensitivity and specificity of these findings are less robust as the cause of coma becomes more heterogeneous and therefore clinicians should evaluate the multiple factors contributing to a patient's state.

Somatosensory evoked potentials measure the cortical response to a peripherally provided sensory stimulus. Absent or delayed waves between the stimulus and recording electrode suggest anatomic disruption in the conduction pathways. Evoked potentials are not affected by sedative administration or environmental electrical noise, but, intracranial lesions may alter the evoked potential signal. In children with coma due to multiple etiologies abnormal sensory evoked potentials (SEPs) predicted unfavorable outcome with sensitivity of 75 % and specificity of 92 % [33]. On initial testing, abnormal SEPs have a PPV for unfavorable outcome of 98 % when absent bilaterally and PPV for favorable outcome of 91 % when present [34]. In children who were comatose from cardiac arrest 24 h after resuscitation, the finding of bilateral absent N20 waves on the SEP had 100 % PPV for unfavorable outcome, with 63 % sensitivity [31]. While N20 SEPs are highly sensitive for poor outcome, the presence of N20 SEP's is not sensitive for favorable outcome. Visual evoked potentials (VEP) use a flickering light to activate the visual system and have mixed results. Small series of patient suggest that absence of VEP may predict death, but presence of VEPs may not predict good outcome [37, 38].

Neuroimaging

Neuroimaging may be helpful for prognosis following certain disease conditions. Following hypoxic ischemic injury and cardiac arrest, magnetic resonance imaging (MRI), especially diffusion weighted imaging (DWI), can characterize the location and severity of injury. Injury to the basal ganglia and watershed regions are highly sensitive for poor outcome [39, 40]. Following adult traumatic brain injury MRI findings of diffuse axonal injury, thalamic injury and ischemic injury are associated with more severe outcomes [41]. DAI is associated with poor outcome when located in the brain stem [42]. In children, lesions in the pons or caudal medulla were associated with 100 % mortality [43].

Newer MR imaging techniques have been useful in predicting outcome after TBI. Susceptibility weighted MR imaging detects hemorrhagic diffuse axonal injury particularly well, and in children with TBI the lesion volume using this technique accounted for 32 % of the variance in cognitive performance [44]. MRS determines metabolic ratios in specific brain regions and may allow the clinician to determine the impact of ongoing metabolic injury.

Conclusion

Coma refers to an abnormality in consciousness in which both wakefulness and awareness are disturbed. There are many etiologies for coma including those that primarily neurologic or those that secondarily affect the brain. Coma is a medical emergency. The history, physical examination, laboratory analysis, imaging, and electrophysiological evaluation may disclose the etiology of coma, allowing specific treatment. A tiered evaluation should rapidly take place to identify and treat reversible causes and to prevent secondary injury. Prognosis of outcome from coma is dependent on etiology and thus prognostic information should not be provided for the family until the etiology is determined. The combined expertise of intensivists and neurologists, while taking into account the views of a patient's family, can help guide the long term care and outcomes of these children.

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