Approach to a child with depressed level of consciousness and coma

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Altered mental status and coma can be considered as an acute neurological emergency characterized by significant brain impairment, necessitating a rapid, methodical approach to evaluation and treatment. There are several, diverse causes of coma, which makes an exact diagnosis challenging. Regardless of the etiology, coma is suggestive of a primary insult to the brain, which, if left untreated, can rapidly progress to secondary injury, and thus result in substantial morbidity and even mortality. It is imperative to rapidly recognize this entity, institute appropriate treatments and improve prognosis. In this article, we review the pathophysiology of coma and its causes to get a basic understanding of this entity. We also discuss the various diagnostic and management approaches for timely recognition and treatment of this life-threatening emergency. In addition, we present some prognostic indicators in a comatose child.

Coma is a nonspecific manifestation of diffuse brain impairment and can result from a structural or metabolic (or a combination of both) cause. Coma usually indicates a primary insult to the brain, which, if left untreated, can rapidly progress to secondary injury, and thus result in substantial morbidity and even mortality. It is imperative to rapidly recognize coma, institute appropriate treatments and improve prognosis.

To better understand the etiology and management of coma, a brief overview of the physiology of neurological processes that are responsible for normal consciousness is necessary. The normal conscious state can be subdivided into a state of arousal or wakefulness, and a state of the awareness of the self and environment. Arousal is the result of sensory stimulation of ascending reticular activating system (ARAS) in the brainstem, with subsequent spread to the hypothalamus, thalamus and, eventually, the cerebral cortex. These, in turn, send numerous positive feedback signals back to the same reticular nuclei to activate them further. Thus, there is self-sustenance secondary to all the positive feedback activity. Therefore, it is clear that complex interplay of these pathways, within themselves and the periphery, is responsible for conscious awareness [1].

Pathophysiology

From the above discussion it is clear that both of the components involved with arousal (i.e., the cerebral cortex as well as the ARAS) must be preserved for normal consciousness. Principal causes of coma can therefore be owing to widespread damage in both cerebral hemispheres secondary to ischemia, or trauma, or suppression of cerebral function by drugs, toxins, hypoxia or systemic metabolic derangements, as in hypoglycemia, uremia or hepatic failure, and brainstem lesions that cause damage to ARAS.

Definitions

Coma is defined as a pathological state of deep and sustained (>1 h) unconsciousness, distinguishable from normal sleep by the inability to be aroused [2,3]. It can also be considered as a state of complete loss of arousal to any kind of stimulation and complete loss of awareness of the self and the surrounding. While coma represents the most severe case of altered sensorium, the following are some of the terms commonly used to describe a patient's altered mental status with reduced alertness, in contrast to hyper-alertness as exemplified by delirium, delusions and hallucinations [3]. The term lethargy indicates drowsiness or decreased wakefulness, characterized by confusion and an ability to communicate if an appropriate stimulus is applied [3]. The term stupor is used to describe a state worse than lethargy and is characterized by significantly decreased responsiveness, but arousability with noxious stimuli [3]. The term obtundation is used to describe a deeper state of unresponsiveness, when the patient is unable to respond to even vigorous stimulation [3]. Since these entities are very subjective and examiner-dependent, thereby rendering them obsolete, it therefore necessitates the use of validated measurement scores, such as the Glasgow Coma Score (GCS), and its

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modification for the pediatric population to objectively and accurately describe the level of change in the mental status of a patient.

Although certain chronic conditions may resemble coma, there are distinct characteristics that allow a physician to differentiate them from acute causes of altered mental states. Vegetative state is characterized by complete loss of awareness of the surrounding; however, there may be some preservation of sleep–wake cycles and spontaneous eye opening. There may also be exhibition of reflex and nonpurposeful movements that are elicited by external stimulation. This state is considered to be permanent if it persists for more than 1 year in patients with a traumatic brain injury or more than 3 months in patients with nontraumatic brain injury [3]. A minimally conscious state can be differentiated from a vegetative state by the presence of purposeful, nonreflexive movements, the presence of some affective and emotional responses to the content of conversation, and the ability to partially fixate and follow visual stimuli [4]. Locked-in syndrome is characterized by presence of an intact consciousness, but inability of expression due to paralysis of voluntary muscles. Voluntary eye movements and blinking may be retained. This condition is often seen in post-traumatic states, pontine lesions and as a sequel of acute neurologic conditions such as Guillain Barré syndrome [5–9]. Akinetic mutism, a qualitatively different condition, is characterized by very slow and delayed motor response, and is usually secondary to lesions in the frontal lobe, responsible for initiating movements, but otherwise has the same characteristics as locked-in syndrome. There is usually preservation of tone and reflexes.

It is important to recognize that all of the abovementioned chronic conditions, except vegetative states and coma, are characterized by preservation of pain perception, and therefore adequate pain control should be an integral part of patient management. Brain death is the final stage in the severity scale for altered mental states, and is characterized by severe coma, and irreversible loss and destruction of cortical and brainstem functions, with no evidence of any arousal, awareness or pain perception [10].

Causes of coma

There are many causes of coma and altered mental state (**Boxes 1 & 2**). These etiologies could either function alone or in combination to result in altered mental states and coma. The impairment is, again, either primary, for example, due to direct brain involvement, or secondary, for example, brain involvement as a result of a systemic insult. The impairment can also be classified as functional (absence of structural brain damage) or organic (presence of structural brain damage). Either mechanism can result in diffuse cortical and brainstem depression. At the molecular level, these impairments are represented by necrotic and apoptotic brain cell death [3]. Various mechanisms proposed to be involved with cell death are excessive release of excitatory neurotransmitters, loss of ion homeostasis, elevated intracellular calcium and mitochondrial and inflammatory free radical production, DNA cleavage, proteolysis and lipid peroxidation [11].

The incidence of coma from various causes is approximately 0.3%. Younger children are more likely to have coma/altered mental states owing to nontraumatic etiologies as compared with older children, where traumatic brain injury is more likely. Among all the etiologies, traumatic brain injury leading to coma deserves a special mention, because head injuries in children are extremely common and account for a large percentage of serious morbidity and mortality. Traumatic brain injury accounts for over 80% of fatalities recorded in the US National Pediatric Trauma Registry [12].

Approach to managing a child with altered mental status & coma

The approach to a comatose patient has four broad components, consisting of:

- Initial stabilization, history, physical examination and rapid neurologic assessment
- Use of reversal agents to treat certain metabolic and toxic derangements
- Determination of the level of CNS function and the etiology of coma
- Institution of specific treatment

It is important to realize that these components are to be addressed simultaneously, rather than in a sequential manner. It is also important to understand some conceptual differences in the management of children versus adults. Children respond differently to adults. Young children might not be able to describe symptoms or localize pain. Such inability of communication leads to a challenging situation, which may need significant experience and patience on the part of the examiner. Anatomically, the head occupies a larger relative body surface area and mass than that of an adult. The CNS of children younger than 3 years is in a state of dynamic development. Increase in the head

Box 1. Etiologic classification of coma and altered mental status .

Infection

- Viral: encephalitis
- Bacterial: meningitis, brain abscess, emphysema, sepsis
- Fungal: meningitis

Metabolic

- Hypoglycemia
- Inborn errors of metabolism
- Dyselectrolytemia: hypernatremia, hyponatremia
- Mineral metabolic defect: hyper/hypocalcemia, hypomagnesemia, hypophosphatemia
- Hyperammonemia
- Hepatic failure: hyperammonemia
- Renal failure: uremia
- Endocrinopathies: hyper/hypothyroidism, adrenal insufficiency
- Addison's disease
- Vitamin deficiency: nicotinic acid, pyridoxine, thiamine
- Intussusception encephalopathy
- Methhemoglobinemia
- Porphyrias
- Mitochondrial encephalopathy

Toxic/ingestions

- Alcohol
- Anticholinergics
- Antihistamines
- Barbiturates
- Benzodiazepines
- Carbamazepine
- Carbon monoxide
- Cocaine
- Cyanide
- Heavy metals (lead)
- Lysergic acid diethylamide (LSD)
- Marijuana
- Narcotics
- Organophosphates
- Phenothiazines
- Salicylate
- Hepatic failure secondary to toxins: amanita mushrooms, acetaminophen

Trauma

- Concussion
- Cerebral contusion
- Hematoma: subdural, epidural, subarachnoid
- Diffuse axonal injury
- Intraparenchymal hemorrhage
- Intraventricular hemorrhage
- Brainstem injury

Structural

- Hematoma: epidural, subdural
- Brain abscess
- Brain cyst
- Brain tumor
- Hydrocephalus
- Hydrocephalus with shunt malfunction

Adapted from Tables 41–48 in [18].

Box 1. Etiologic classification of coma and altered mental status (cont.).
Vascular
• Embolism
• Hemorrhage: subarachnoid, intraparenchymal
• Vasculitis
• Lupus
• Hypertensive encephalopathy
Hypoxic
• Respiratory failure
• Cardiac: dysrhythmia, arrest, cardiogenic shock
• Toxins: carbon monoxide, cyanide
• Near drowning
Epileptic
• Post-ictal states
• Status epilepticus
Psychologic
• Conversion disorder, catatonia
Adapted from Tables 41–48 in [18].

circumference in the first year reflects increasing brain volume. The pediatric brain undergoes doubling of its weight by 6 months of life, and by 2 years it is almost 80% of adult brain weight. This is also the time when there is active and ongoing myelination, synapse formation, dendritic arborization and increasing neuronal plasticity taking place, and therefore any injury to the brain at this time can lead to arrest of these processes and cause significant deficits [13,14]. As compared with adults, children also demonstrate exaggerated cerebrovascular response to injury, and therefore are more prone to develop diffuse brain swelling more readily [15]. The brain parenchyma of children is minimally compressible, contributing minimally to an intracranial volume buffering system, as compared with cerebrospinal fluid (CSF) and cerebral blood volume in situations leading to increased intracranial pressure (ICP), and therefore a rapid recovery is often experienced in children with no significant brain lesion, in whom optimal cerebral perfusion pressure (CPP) is maintained throughout the disease process.

Prehospital care

The management of a child with a depressed level of consciousness and coma should ideally begin in the prehospital setting. There has been significant research pertaining to prehospital management, especially concerning critically injured patients, whose best chance of survival is dependent upon receiving high-quality care from the earliest possible postinjury moment. This high-quality care is expected from the providers of prehospital care. The recommendations made by prehospital trauma life support have shown favorable results and provide guidelines for prehospital management of traumatic brain injury. These include the following [16]:

- The need for endotracheal intubation in a child or adult with GCS of equal to or less than 8;
- Maintenance of adequate oxygenation, assisting normoventilation at rates of 20/min for children, and 25/min for infants;
- Control of external hemorrhage;
- Intravenous fluid resuscitation to maintain systolic blood pressure greater than or equal to 90 mmHg;
- Treatment of seizures with benzodiazepines
- Assessment of blood glucose levels;
- Recognition of the signs of increased ICP, such as decrease in GCS by 2 points, fixed or nonreactive pupil, hemiparesis or hemiplegia and Cushing's triad (irregular breathing, bradycardia and hypertension);
- Initiation of corrective measures, such as considering removal of cervical collar, sedation and paralysis of patient, osmotherapy and mild hyperventilation;
- Safe transportation of the patient to a trauma center, with the availability of CT scan and neurosurgical services.

Initial stabilization

The approach to the management of a comatose child involves an immediate and rapid assessment of the 'A, B, Cs' – Airway, Breathing and

Box 2. Age-based etiologies of coma.

Neonate
- Congenital anomalies
- Hypoxic ischemic injury
- Hypoglycemia
- Inborn errors of metabolism
- Hypocalcemia
- Seizures
- Congenital infection
- Sepsis
- Intraventricular hemorrhage

Infant
- Infection: meningitis/encephalitis
- Trauma: accidental and nonaccidental
- Shock: hypovolemic, cardiogenic and septic
- Metabolic: hypo/hypernatremia, hypoglycemia, inborn errors of metabolism
- Ingestions: accidental or nonaccidental (child abuse)
- Seizures
- Intussusception

Child
- Trauma
- Infection: meningitis, encephalitis, brain abscess
- Ingestion
- Metabolic: hypoglycemia, diabetic ketoacidosis
- Seizure

Adolescent
- Trauma
- Infection: meningitis, encephalitis
- Ingestion
- Seizure
- Psychologic

Adapted from Tables 41–49 in [18].

hemodynamics, especially ketamine (which is known to cause an increase in ICP) or pentobarbital (which is known to reduce systemic blood pressure, thus potentially reducing CPP) may be harmful during rapid sequence induction for airway control. Rapid assessment of the circulatory status (capillary refill and blood pressure) and aggressive efforts to restore normal circulatory volumes may be required. Interventions such as intraosseous needle placement should be encouraged if immediate access to the vascular system is problematic or considered time-consuming. Additionally, the possibility of a cervical spine injury along with head injury should always be entertained in all children who present with altered mental state, and patients should have their cervical spine stabilized by in-line traction. A rapid neurological evaluation should be performed to establish the patient's level of consciousness, as well as papillary size and reaction. The AVPU method is a simple mnemonic to describe the level of consciousness:

- A: Alert
- V: Responds to Vocal stimuli
- P: Responds only to Painful stimuli
- U: Unresponsive to all stimuli

A decreased level of consciousness may suggest decreased cerebral oxygenation and/or perfusion, or may be owing to direct cerebral injury and indicate a need for immediate re-evaluation of a patient's oxygenation, ventilation and perfusion status. The patient should also be completely undressed to facilitate thorough examination and assessment. Care must be taken to avoid hypothermia from undressing the patient.

History

After initial stabilization is achieved, a brief interview with the child's parents/care providers, along with circumstances leading to the alteration of mental status, should be sought. Pertinent historical details, such as rapidity of onset, specific symptoms and signs (toxidromes) may provide valuable clues to the etiology and aid in subsequent management of the patient. An acute presentation in an otherwise normal individual may be suggestive of etiologies such as acute trauma, metabolic disorders, cardiac dysarrhythmias or intoxication. Etiologies that cause progressive or gradual alteration of mental status over a period of days often have limited scope for acute reversal treatment, but still need comprehensive evaluation. Any knowledge of underlying pathology, such as pre-existing conditions (for example

Circulation – to ensure adequacy of oxygenation, ventilation and tissue perfusion, respectively. Before determining specific etiologies, ordering specific tests or providing specific medications, care should be taken to ensure that the patient's airway is secure. If not secure, the patient may require airway repositioning, supplemental oxygenation and suctioning of oropharyngeal secretions. Following this, the adequacy of breathing must be assessed. Patients may require support of their breathing by assisted ventilation in the form of a bag and mask, or even endotracheal intubation (often carried out with rapid sequence induction). Intubation should also be performed as an intervention to facilitate hyperventilation in an attempt to reduce intracranial hypertension, or in cases where the patient has significant hypoventilation, in instances of opioid intoxication. The provider should recognize that use of certain medications that alter the intracranial

diabetes mellitus, inborn errors of metabolism), in the patient could also prove to be a vital piece of information for further analysis and treatment [17]. The AMPLE history is a useful mnemonic to obtain complete historical details:

- A: Allergies
- M: Medications currently used
- P: Past illnesses/Pregnancy
- L: Last meal
- E: Events/Environment related to the patient's status

Physical examination

Every vital sign of the patient should be carefully inspected and interpreted, as they may offer extremely valuable information to guide immediate treatment. For example, an elevated temperature could indicate systemic infection (bacteremia or septicemia), intracranial infection (meningitis, encephalitis or intracranial abscess), a post-ictal state or drug ingestions (anticholinergics), heat stroke or pontine hemorrhage. Hypothermia may suggest ingestions (alcohol, opiates), fulminant infections (septicemia, especially in very young infants) and environmental exposures (frost bite, submersion accidents). Bradycardia could suggest ingestions (β-blockers, calcium channel blockers) or can be a component of Cushing's triad, suggestive of increased ICP. Tachycardia in a comatose child, on the other hand, can be secondary to pain, fever, dehydration, shock (hypovolemic, septic or cardiogenic), or ingestions (anticholinergics and sympathomimetics). Tachypnea could indicate central stimulation of the respiratory center with drug intoxications such as salicylate, or as a compensatory mechanism for metabolic acidosis (e.g., Kussmaul's breathing associated with diabetic ketoacidosis). Hypoventilation, characterized by slow, shallow breathing, may suggest intoxication with opiates or other agents that depress the CNS (alcohol, sedative hypnotics). Specific breathing patterns in regards to its rate, depth and cycling can suggest the presence of certain pathologies. Cheyne–Stokes respiration, characterized by periods of hyperpnea alternating with apnea, is observed in bilateral hemispheric and diencephalic dysfunction, and may herald the occurrence of transtentorial herniation. Apneustic breathing, seen in lesions involving the mid to lower pons, is characterized by prolonged pause at full inspiration. Low pontine and upper medullary lesions are associated with clusters of breath, alternating with periods of apnea, also known as ataxic breathing, which progresses to agonal breathing with medullary lesions. Hypotension, suggestive of shock states and intoxications such as accidental or intentional overdose of antihypertensives such as clonidine, β-blockers and calcium channel blocker medications, is a helpful parameter for interpretation in combination with other vital signs, as is hypertension, which may occur secondary to intoxications or as a feature of Cushing's triad.

Other components of the physical examination include inspection of the skin for color, lesions, rashes, pigmentation or needle tracks. These findings can suggest intoxications, infections, illicit drug use and metabolic impairments. Skin erythema may suggest carbon monoxide or mercury poisoning. Cyanosis may be encountered in patients with hypoxia, or due to the presence of a congenital cyanotic heart lesion (which predisposes the patient to strokes and other cerebrovascular accidents) or ingestions that cause altered sensorium and methhemoglobinemia, which may result from toxic exposures such as aniline or severe diarrheal illness in infancy. Petechia may be seen with infectious endocarditis, sepsis, disseminated intravascular coagulation or trauma (child abuse). An alteration in pigmentation (hyperpigmentation) could suggest Addison's disease, and needle tracks suggest intravenous drug use. Breath odor can be used to pinpoint etiologies such as diabetic ketoacidosis (fruity odor), alcoholic intoxication and cyanide poisoning (bitter almonds). Examination of the eyes, ears and nose, with particular attention to any bruising around the eye and any drainage from the ears or nose, indicative of CSF otorrhea or rhinorrhea, can offer diagnostic clues for fractures and nonaccidental trauma. Fundoscopic evaluation is important to detect the presence of papilledema or retinal hemorrhages (seen in nonaccidental trauma). Oral examination can reveal tongue lacerations suggestive of injury secondary to a seizure. Head examination, especially palpation of the anterior fontanel, is often helpful to determine raised ICP.

Role of reversal agents

While the evaluation is in progress, the physician must be vigilant regarding the possibility of immediately reversible causes of the coma, and hypoglycemia and opioid intoxication should be considered in the differential. Hypoglycemia can be immediately reversed by administering a 25% dextrose solution (dose: 0.5–1 g/kg) as a rapid,

intravenous push. Opioid intoxication can be reversed, as well as detected, by administering intravenous naloxone 0.1 mg/kg up to 20 kg for those up to the age of 5 years and 2 mg for those over 5 years of age. Naloxone can also be administered subcutaneously and intramuscularly. The administration of flumazenil 0.2 mg intravenously over 30 s can reverse benzodiazepine intoxication. The physician should be aware that flumazenil can precipitate refractory seizures in patients with chronic benzodiazepine exposure. Only in the presence of obvious etiology such as trauma is there a rationale for not using these agents for immediate intervention. Intravenous access for these medications can also be utilized to sample blood for baseline yet broad-spectrum screening laboratory investigations, such as a complete blood count, serum electrolytes, blood urea nitrogen, creatinine, glucose and calcium levels. At our institution we routinely collect blood for a rapid bedside glucose test, as well as capillary blood gas evaluation for quick assessment of acid–base status, while awaiting the laboratory results. Liver function tests, coagulation profile, serum ammonia, osmolality, carboxyhemoglobin, basic serum and urine toxicological screens can also be obtained when specific etiologies are under consideration.

Neurological examination

Upon stabilization of the patient, the physician must perform a detailed neurological evaluation to determine a specific etiology and depth of alteration of sensorium, and also to guide further evaluation, specific laboratory workup and imaging modalities to determine the diagnosis. The detailed neurological examination (including assessment of pupils, fundus, cranial nerves, motor and sensory evaluation) should be performed to help localize the site of the lesion in the CNS.

The preservation of pupillary reflexes suggests the presence of metabolic encephalopathy, and their absence suggests structural pathologies, an exception being intoxication with atropine-like medications, which results in fixed, dilated pupils [18]. Pupillary size and response is dependent on the balance between sympathetic and parasympathetic stimulation. The sympathetic response dilates the pupil, whereas the parasympathetic response causes constriction. Parasympathetic fibers originate in the Edinger–Westphal nuclei in the midbrain and accompany the oculomotor nerve along its long path, whereas the sympathetic nerves originate in the hypothalamus and traverse through the cervical spinal cord and cervical sympathetic chain to eventually innervate the pupillodilator muscles of the eye, sweat gland of the face and the Muller's muscle of the eyelid. Lesion in the parasympathetic nuclei or fibers results in an ipsilateral fixed, dilated pupil. Clinically, this entity is suggestive of ipsilateral uncal herniation, and therefore should be treated as a surgical emergency. Lesions anywhere along the pathway of sympathetic input can result in ipsilateral pupillary constriction (miosis), ptosis with secondary enophthalmos and anhydrosis, also known as Horner's syndrome. Unequal pupils (anisocoria) signify direct injury to the eye or disruption of unilateral sympathetic or parasympathetic signals. Injury to nuclei in the midbrain affects both autonomic pathways and may result in neutral, fixed pupils. Lesions in the tectum and midbrain may cause slightly large, but fixed pupils. Due to preservation of accommodation, papillary size may vary, resulting in the clinical entity called hippus. Pontine lesions disrupt the sympathetic pathways, resulting in pinpoint pupils, which are classically seen in pontine hemorrhage. Metabolic and toxic encephalopathies are responsible for small and minimally reactive pupils. Symmetrically dilated and responsive pupils are seen with anticholinergic toxicity, whereas severe anoxic injuries result in dilated and unresponsive pupils.

Assessment of extraocular movements is the next important component of evaluation of a comatose child. The extraocular movements are facilitated by complex interplay of several different neuronal pathways. The frontal lobes control voluntary eye movements, the rapid phase of nystagmus and also influence brainstem reflexes that determine eye movements. The oculomotor nerve (third cranial nerve) and trochlear nerve (fourth cranial nerve), which originate in the midbrain, and abducens nerve (sixth cranial nerve), which originates in the pons, control the extraocular muscle movements. Conjugate eye movements in the horizontal plane are coordinated between ipsilateral oculomotor nuclei and contralateral abducens by the medial longitudinal bundle. Proprioceptive and vestibular inputs also coordinate eye movements. Complex yet smooth coordination between these pathways forms the basis for oculocephalic or 'doll's eye' reflex and the oculovestibular reflex testing. These influences are responsible for maintenance of visual fixation despite movements of the head. In a comatose child, an oculocephalic reflex is

considered abnormal if eyes do not move in the opposite direction of head movement, either from one side to the other or up and down. If there is a concern for cervical spine injury, this testing is absolutely contraindicated, and the same pathways can be assessed by performing the oculovestibular reflex or caloric response test. Irrigation of one external ear canal with warm or cold water induces convection currents in the endolymph of the semicircular canals. In an awake person, nystagmus is elicited with a slow component towards the ear irrigated with cold saline and fast component away from the stimulus. The fast component response to cold or warm stimulus is the basis of the mnemonic 'COWS' (cold, fast component opposite, warm, fast component towards the ear tested). In a patient with a brainstem lesion with disruption involving pathways between vestibular and abducens nuclei, both the oculovestibular and oculocephalic reflexes are absent. Conversely, presence of these reflexes in a comatose child indicates the intactness of the brainstem and midbrain pathways.

Corneal reflexes test the integrity of pathways that include the afferents carried by the trigeminal nerve (fifth cranial nerve), and the response exhibited by upward movement of the eye mediated by the oculomotor nerve and, more importantly, closure of the eyelid mediated by the facial nerve (seventh cranial nerve). The presence of this reflex is reflective of intact pathways between the midbrain and the pons. This reflex loses its value in a sedated and paralyzed patient, but is of significance by its absence in a metabolic disorder with profound coma. Intact gag reflex indicates integrity of glossopharyngeal and vagal afferents.

The next step is examination of the motor system and starts with simple observation of patient's posture, evidence of spontaneous activity and response to various stimuli. Asymmetrical postures may suggest hemiparesis or hemiplegia from contralateral structural lesions to the cortico-spinal tracts. Hypertonia may be suggestive of acute brainstem injury at the level of midbrain and pons. Acute hypotonia or flaccid weakness is a hallmark of lower pontine, medullary or spinal cord lesions. Responses to noxious stimulation, such as purposeful withdrawal and vocalization helps the examiner to assess neurological status, and may also aid in the gradation of patients as regards to neurological assessment scales. Decorticate posturing characterized by flexion of arms and extension of legs indicates a bilateral lesion between the midbrain and the cerebral cortex. On the other hand, decerebrate posturing characterized by hyperextension, with or without opisthotonus, is suggestive of lesion in the midbrain pontine region or severe brainstem compression. Another important aspect of evaluation is to obtain assessment of a patient's ICP and whether there is evidence of any herniation. Most herniation syndromes pose acute risk of brain death and should be considered as dire emergencies, and emergent medical and surgical interventions should be instituted promptly. Uncal herniation is characterized by ipsilateral fixed and dilated pupil and ipsilateral ophthalmoplegia, and may also result in hemiparesis by compression of cerebral peduncle. Central herniation syndrome is secondary to a more generalized process such as cerebral edema, resulting in increased ICP, with compression of subcortical structures and cerebellar herniation through the foramen magnum. Clinically, physical findings evolve and vary as the severity and level of herniation progresses. With herniation of midbrain and upper brainstem, the patient will exhibit decorticate posturing with small pupils. Brainstem reflexes may be preserved. These are the patients that exhibit the classic Cheyne Stokes respirations. As lower brainstem and pons start becoming compressed, the patient starts getting decerebrate posturing, with pupils becoming more dilated, and generalized diminished responses accompanied by loss of brainstem reflexes. Cheyne Stokes respirations will be replaced by more rapid and regular breathing. Once the lower pons and medulla are involved, there is complete loss of brainstem reflexes, with the patient assuming a flaccid posture and respirations becoming very slow and irregular, before resulting in a complete cessation.

Motor responses, along with verbal and ocular responses, are important cortically determined aspects of consciousness, assessed by rating scale scores, such as the GCS, and its modification for use in children (Table 1). These measures do not take into account every aspect of neurological examination, but its components have proven to have descriptive and prognostic value.

Neurological examination in herniation syndromes

Localized mass lesions or increased ICP can cause several important cerebral herniation clinical syndromes. Uncal herniation is most often owing to a local mass lesion or swelling, which pushes the uncus through the tentorial notch

Table 1. Glasgow Coma Scale scoring and modification for children.

Activity	GCS for adults	GCS modified for children	GCS for infants	Score
Eye opening	Spontaneous	Spontaneous	Spontaneous	4
	To speech	To sound	To sound	3
	To pain	To pain	To pain	2
	None	None	None	1
Verbal response	Oriented	Age-appropriate oriented, smile	Coos and babbles	5
	Confused	Confused, aware of environment	Irritable, cries	4
	Inappropriate words	Irritable, inconsistently consolable	Cries in response to pain	3
	Nonspecific sounds	Inconsolable, unaware of environment, agitation	Moans in response to pain	2
	None	None	None	1
Motor	Follows commands	Obeys commands, spontaneous movements	Moves spontaneously, purposely	6
	Localizes pain	Localizes pain	Withdraws to touch	5
	Withdraws in response to pain	Withdraws in response to pain	Withdraws to pain	4
	Flexion in response to pain	Flexion in response to pain	Decorticate posturing to pain	3
	Extension in response to pain	Extension in response to pain	Decerebrate posturing	2
	None	None	None	1

Best total score = 15.
Adapted from [3,43–45].
GCS: Glasgow Coma Score.

and progressively compresses the ipsilateral oculomotor nerve, initially affecting the parasympathetic pupillomotor fibers running along its surface and resulting in a sluggishly reactive then fixed and dilated pupil. Further compression of the oculomotor nerve causes partial ophthalmoplegia, with the affected eye turned outward and downward owing to unopposed functioning of the lateral rectus and superior oblique muscles. Ipsilateral hemiparesis can also occur due to compression of the contralateral cerebral peduncle by the tentorial notch.

Central herniation is most often due to diffuse brain edema or obstructive hydrocephalus, which causes increased ICP, with movement of the thalamus and hypothalamus downward through the tentorial notch and of the cerebellar tonsils through the foramen magnum. Compression and ischemia of the diencephalon and brainstem can occur in a slow rostrocaudal progression or can advance abruptly to give signs of lower brainstem injury. With a diencephalic-level injury, comatose patients have decorticate posturing, Cheyne-Stokes respirations, and small pupils, but have preserved brainstem reflexes and remain able to localize noxious stimuli. With involvement of the midbrain and upper pons, posturing becomes decerebrate, pupils become midposition in size and sometimes irregular in shape, and there is a loss of pupillary, oculocephalic and oculovestibular reflexes. Respirations may become regular and rapid. With involvement of the lower pons and medulla, all brainstem reflexes are lost, posturing is replaced with a flaccid paralysis and respirations become ataxic, irregular and slow, before eventually ceasing.

Investigating a comatose patient

As discussed earlier in the article, evaluation of coma requires significant multitasking with respect to history, physical examination and simultaneous attempt at determining the etiology of coma. Laboratory testing that can be utilized for evaluation of comatose patient can be divided into three broad categories:

- Immediate bedside testing with a turnaround time of 1–2 min
- The second group of tests, being tests that have a turnaround time of 30–45 min, which is when the patient is being resuscitated
- Tests whose results may not be available for several hours to days, and very rarely impact acute resuscitation and stabilization measures

In the first set of laboratory investigations, the most widely utilized one is the bedside glucose measurement, which, if indicative of hypoglycemia, can lead to reversal of coma by administration of intravenous dextrose bolus. Most hospitals, including the authors', utilize capillary blood gas with electrolyte measurement, which, apart from offering rapid valuable information

regarding acid–base status, is also capable of measuring electrolytes, lactic acid, carboxyhemoglobin level and ionized calcium levels with fair accuracy. The second set of laboratory investigations include a complete blood count and a metabolic profile that includes serum electrolytes, glucose, blood urea nitrogen and creatinine, serum calcium, basic liver function tests, coagulation profiles, osmolality, serum ammonia and lactate levels. The complete blood counts are helpful in detecting leukocytosis, indicating infection or stress, anemia and thrombocytopenia, indicating the possibility of intracranial bleeding, polycythemia and thrombocytosis, which could suggest stroke syndromes. Abnormalities of electrolytes and renal and hepatic function can aid in detecting metabolic derangements, as well as uremia and hepatic injury from conditions such as sepsis, shock or intoxications. High levels of ammonia and lactate can lead to diagnoses of inborn errors of metabolism, hepatic failure, and toxic and metabolic encephalopathy. The metabolic profile can also include screening for inborn errors of metabolism such as serum amino acids and urine organic acids to screen for disorders of amino acid metabolism and organic acidemias. Screening for fatty acid metabolism can be performed by sending for levels of carnitine and acyl carnitine. Abnormal neurohormonal states can be detected by obtaining thyroid and cortisol levels. A toxicologic screening by obtaining urine and serum drug screens can detect the presence of potential toxicants, such as amphetamines, barbiturates, cocaine, cannabinoids, phencyclidine and propoxyphene in the urine, and acetaminophen, salicylates, tricyclic antidepressants, sympathomimetics and alcohol in the serum. The toxicologic screens are especially of value in acute presentations. The physician should be knowledgeable regarding his or her institutions' toxicologic panels, with regards to the agents that are screened therein. In cases with a very high suspicion level for intoxication, a more elaborate comprehensive toxicologic screening may be necessary. The physician must also be cognizant of cross-reactivities of toxicologic screens with routine over-the-counter medications; for example, use of dextromethorphan, a common ingredient of over-the-counter cough syrup, may result in a positive immunoassay screen for phencyclidine. Cultures from blood, urine and the CSF are obtained if there is suspicion for any acute infection. A spinal tap by lumbar puncture can be deferred if there are signs of increased ICP, impending cardiorespiratory failure, bleeding disorders or local infections. Administering broad-spectrum antibiotics should not be deferred if a lumbar puncture can not be performed and intracranial infections are suspected. Neuroimaging with computed tomogram should preferably be performed prior to lumbar puncture. The physician must always remember to screen for pregnancy in a reproductive age-group female patient. The third group of laboratory investigations is usually nonroutine and often obtained after consultation with specialty services, and does not impact immediate management. These investigations, as mentioned earlier, are geared towards searching for an exact diagnosis to guide treatment further down the line, exemplified by the ceruloplasmin level for detection of Wilson's disease.

A patient with a suspected structural or vascular lesion should undergo emergent computed tomography (CT) of the head. Even though there are concerns of radiation exposure, CT has been shown to be a very practical imaging modality, especially in an unstable patient, and has rapid turnaround times and acceptable sensitivity for acute intracranial lesions such as fractures, hemorrhage, tumor and herniation syndromes. A normal CT scan in a comatose patient may suggest metabolic or toxic etiologies. Repeat CT scanning is indicated in patients with clinical deterioration for detection of edema, hemorrhage or herniation. MRI takes precedence over CT when the patient is reasonably stable and can afford to spend some time in the MRI suite, as the average time for acquisition of accurate brain MRI is approximately 30 min. However, it offers distinct advantages over CT in the detection of parenchymal abnormalities, with improved accuracy and more structural detail such as gray–white matter differentiation or nondifferentiation as in axonopathies and myelinolysis [19,20].

Electroencephalogram (EEG) testing is important in a comatose patient, especially to detect an entity known as nonconvulsive status epilepticus [21], which is characterized by seizure activity in the brain that is not clinically apparent in sedated and paralyzed patients and may guide the physician to treat a patient with antiepileptic medication. Certain EEG patterns, such as temporal lobe seizure activity, can be an indicator in the diagnosis of herpes encephalitis. Serial EEGs may also prove to be of value for prognostication of the patient.

Electrocardiogram should be performed on all comatose patients to detect abnormalities such as widened QRS, suggestive of tricyclic antidepressant exposure.

Management of coma

As discussed earlier, a coma state in a patient is suggestive of a primary injury to the brain, which, in the absence of prompt therapy, puts the patient at risk for secondary injury, owing to various detrimental factors such as systemic hypotension, hypoxia, respiratory failure and worsening cerebral edema and progressive herniation. Thus, secondary injury heralds a downward spiral for the patient and therefore has a poorer outcome. The management of coma takes into account mechanisms of cell injury, aims to preserve neurological function, prevent secondary injury and optimize regeneration and recovery. The major components of management include normalization of circulation and respiration, fluid management, maintenance of optimal CPP and treatment of seizures (Box 3).

Once the airway is secured and breathing is confirmed to be effective, attention should next be focused upon management of intracranial hypertension and prevention of secondary injury. At this point, the patient should have at least two large bore intravenous accesses, or an intraosseus approach if it is not possible to obtain intravenous access. The purpose of generous intravenous or vascular access is to maintain adequate cardiac output and tissue perfusion, more specifically, cerebral perfusion. Fluid resuscitation should be instituted to optimize end-organ perfusion, and if that alone does not achieve desired results, use of inotropic agents should be considered. The monitoring of serum electrolytes and urine output serves as a helpful guide in assessing circulatory status.

Fluid restriction has a role only if there is suspicion of syndrome of inappropriate secretion of antidiuretic hormone.

Maintenance of a CPP at or above 50 mmHg is strongly correlated with survival after traumatic brain injury [22]. Pediatric literature suggests that the goal of maintenance of CPP in nontraumatic brain injury should be at or above 40 mmHg in infants and toddlers, at or above 50 mmHg for young children and at or above 60–70 mmHg for older children and adolescents. Previous practice of maintaining patients at risk for cerebral edema in a mild negative fluid balance has shown to be of less benefit with respect to outcome when compared with therapy comprising carefully titrated fluids and medication to maintain optimum mean arterial pressure and CPP and, indirectly, the ICP [23]. The relationship between these variables can be clearly demonstrated by the following equation:

CPP = Mean arterial pressure – ICP

Reduction of intracranial hypertension for maintenance of optimum CPP forms the cornerstone of treatment of comatose patients at risk of herniation from intracranial hypertension. A patient suspected to be at risk for herniation should have an emergent CT scan performed to evaluate for structural lesions that may be responsible for increased ICP. If there is evidence of swelling of the brain, monitoring of ICP is indicated. The goal is to maintain ICP below 20 mmHg, and patients may benefit from immediate surgical decompression procedures. ICP monitoring is usually not initiated in the emergency department. Children in need of ICP monitoring should be admitted to a pediatric intensive care unit. The first step in ensuring reduction of intracranial hypertension is securing the airway by endotracheal intubation and mechanically hyperventilating the patient mildly to maintain $PaCO_2$ at 35 mmHg [24]. This intervention will result in just enough cerebral vasoconstriction to help relieve intracranial hypertension. Care should be taken to not hyperventilate excessively, as $PaCO_2$ of 25 mmHg is associated with severe cerebral vasoconstriction and may add insult to the injury by causing severe cerebral vasoconstriction [25,26]. There is also no role for 'prophylactic' hyperventilation for the same reason as mentioned above. The risk of cerebral vasoconstriction can be justified only in patients who have signs of ongoing herniation. Midline head positioning of the patient and head elevation by 30° helps

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Box 3. Steps in the management of coma.

1. Assure a stable airway, adequate oxygenation and ventilation, and circulation

2. Recognize and treat hypoglycemia

3. Consider specific antidotes for medication overdose

4. Monitor for, prevent and treat increased intracranial pressure

5. Evaluate for and treat seizures

6. Correct electrolyte and acid–base imbalance

7. Normalize body temperature

Adapted from [3].

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reduce hydrostatic pressures in the brain by facilitating venous drainage and may contribute to reduction of ICP. As mentioned earlier, reduction of intracranial hypertension can be achieved surgically by removal of the offending structural lesion or placement of ventriculostomy drainage.

Medical therapy constitutes use of osmotic and loop diuretics. Mannitol is an osmotic diuretic that exerts its effect by causing a shift of fluid from the intracellular compartment of the brain into the vascular compartment, thereby helping relieve intracranial hypertension. It can be used in doses ranging from 0.25 to 1 mg/kg, and requires frequent monitoring of the patient's electrolytes and osmolality to watch for and prevent development of iatrogenic dehydration, which in turn may reduce CPP. Recent literature suggests that use of hypertonic saline (3% normal saline) may be beneficial in certain situations where elevated ICP is refractory to conventional treatment. An added benefit is its inability to cause diuresis, thereby decreasing the risk of hypovolemia [27]. Diuretics, such as furosemide (acts on the loop of Henle) have been used in conjunction with mannitol to maintain adequate CPP. Deep sedation, as well as paralysis, helps control intracranial hypertension by preventing any ICP spikes secondary to patient movements. Steroids for reduction of intracranial hypertension have been shown to be beneficial in space-occupying lesions with localized edema, but do not seem to have any benefit in the management of diffuse cerebral swelling. Barbiturate coma has been utilized to reduce ICP and cerebral metabolism, but requires careful monitoring of hemodynamic function in terms of cardiac output and blood pressure.

Treatment of seizures forms an important component of therapy. Benzodiazepines are first-line agents in controlling any initial seizure activity and are often successful in controlling acute seizures. Patients with status epilepticus (seizure activity lasting for more than 30 min), can be initially treated with benzodiazepines, which have rapid onset and short half-life, but need to be followed by longer-acting agents such as phenytoin and phenobarbitol. Phenytoin is nonsedating and does not affect subsequent neurological examination. Phenobarbital, on the other hand, can cause sedation and may affect subsequent neurological examination. Phenobarbital offers a distinct advantage in controlling diffuse seizure activity, such as toxic seizures, over phenytoin, which is more effective in controlling focal seizures. If seizures persist after administration of these antiepileptic agents, they are considered refractory

and warrant institution of repeated dosing of phenobarbital to achieve very high levels for complete cessation of seizure activity. As mentioned earlier, the physician should bear in mind the possibility of nonconvulsive seizure activity in patients who are sedated and paralyzed, and must take care to treat them appropriately. An urgent EEG should be requested in all such cases. Prophylactic treatment with anticonvulsants reduces the risk of early post-traumatic seizures, as well as improving outcomes among children with traumatic brain injury [28–31]. The general consensus among experts is to institute anticonvulsant therapy during the first week following severe traumatic brain injury [32].

Other management components include treatment with broad-spectrum antibiotics in any patient suspected to have systemic or intracranial infection. Frequent electrolyte and acid–base monitoring is important to rule out any imbalances as a result of altered patient physiology and treatment measures. Frequent monitoring of electrolytes and urine output also helps clinicians to detect conditions such as syndrome of inappropriate antidiuretic hormone or diabetes insipidus. The wide fluctuations in fluid intake and losses that these conditions may cause can put the patient at severe risk for secondary brain injury.

Studies on the use of controlled therapeutic hypothermia in a select group of patients have shown some promise, and need to be explored further [33]. There is, however, no question that any increase in the temperature must be aggressively treated to prevent increased cerebral metabolism and demand [34].

Some other supportive components include early nutritional support by hyperalimentation, which have been shown to accelerate neurological recovery [35]. Care should be taken to prevent development of deep-vein thrombosis and secondary pulmonary embolism by using various modalities such as heparin and compression stockings. Early involvement of physical therapy has demonstrated significant improvements in neurological outcome.

Generally, specific management can be facilitated once the presumptive diagnosis is confirmed, with initiation of definitive therapy in the emergency department. Any patient not responding to therapeutic interventions or requiring ongoing monitoring or critical care, or whose diagnosis is still in question after the initial management, needs to be transferred to a pediatric intensive care unit.

Box 4. Glasgow Outcome Scale.
1. Death
2. Persistent vegetative state
3. Severe disability: conscious but disabled
4. Moderate disability: disabled but independent
5. Good recovery
Adapted from [3].

Outcome of coma

Institution of prompt treatment helps to modify the outcome favorably. The prognosis of coma is largely dependent on etiology, with good prognosis for uncomplicated drug intoxications and poor prognosis for hypoxic ischemic encephalopathy. There are scales that measure the outcomes based on recovery and functional independence, as exemplified by Glasgow Outcome Scale (**Box 4**) [36], whereas other measures, such as the Pediatric Cerebral Performance Category Scale (**Box 5**), have more age-appropriate functional performance measures that help to quantify outcomes more accurately [37]. There are also a number of scales that gauge social and emotional responses as additional dimensions for measurement of outcomes. Most surviving patients should undergo serial neuropsychological testing to accurately measure various aspects of neurological recovery.

Box 5. Pediatric Cerebral Performance Category Scale.
1. Normal: normal at age-appropriate level, school-age child attends regular school
2. Mild disability: conscious, alert and able to interact at age-appropriate level, school-age child's grades may not be appropriate for age, mild neurological deficit
3. Moderate disability: conscious, sufficient cerebral function for age-appropriate independent activities. School-age child attending special education class. May have learning disability
4. Severe disability: conscious. Dependent on others for daily activities
5. Coma or vegetative state: any degree of coma, unawareness even if awake in appearance. Cerebral unresponsiveness. No evidence of cortical function
6. Brain death: apnea or areflexia or absence of brain activity on electroencephalogram
Adapted from [3].

Literature on recovery after cerebral events leading to altered mental states/coma suggests that the recovery of motor skills is better when compared with recovery of cognitive skills. This may be related to the fact that children have dynamic neuronal networks and more susceptibility of the neuronal pathways that control cognition as compared with motor skills [38,39].

There is also abundant literature on outcome prediction by means of clinical, radiological and electrophysiological measurements. Patients with an initial GCS of 3 have mortality rates between 50 and 60% after traumatic brain injury, with significant outcome variation depending on the degree and severity of secondary brain injury. Children with a GCS of 4–8 have a significantly higher likelihood of survival [40,41]. A study involving children with nontraumatic brain injury suggested that younger children with lower GCS scores, absent brainstem reflexes, poor motor responses, or hypothermia or hypotension at presentation tend to have poorer outcomes [42]. There have been large numbers of studies that now conclusively prove that the mortality rate is extremely high for children who present to the emergency room in cardiac arrest, regardless of the precipitating event.

Conclusion

Coma in a pediatric patient is a medical emergency that requires rapid and organized intervention. Evaluation of a comatose child consists of initial stabilization of basic life-support needs, airway, breathing and circulation, and simultaneous conduction of effective history and accurate physical examination. Regardless of etiology, there are general principles for the management of coma, which the physician must be familiar with in order to achieve optimal results and outcomes.

Executive summary

- Coma is suggestive of a primary insult to the brain, which, if left untreated, can rapidly progress to secondary injury, and thus result in substantial morbidity and even mortality.
- It is imperative to rapidly recognize this entity, institute rapid and appropriate treatment and improve outcome.

Approach to coma

- It is important to understand the basic pathophysiology of coma.
- It is important to be aware of other clinical states and subjective terminologies that exist to define states of altered mental status.
- The etiologies of coma are numerous and diverse, resulting in either a direct or indirect brain injury.
- Early management includes initial evaluation and treatment, which includes initial stabilization, rapid assessment, use of reversal agents to treat certain metabolic and toxic etiologies, and diagnostic studies, followed by detailed history and physical examination, inclusive of a detailed and specific neurological examination.
- The subsequent management goal is to prevent and treat increased intracranial pressure by judicious use of medications, as well as surgical intervention depending upon the specific etiology.

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