

REVIEW

Clinical approach to coma patients: tips and tricks

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Abstract

The reticular activating system (RAS) is responsible for wakefulness. The RAS projects activation to either side of the hemisphere. The dysfunction of the RAS or insufficiency of its activation results in impairment of consciousness. Physicians classify levels of awareness into four levels, from normal status to most severe unconsciousness, these being alert, drowsy, stupor, and coma, respectively. While the causes of unconsciousness are varied, physicians generally divide them into structural and metabolic etiologies upon the dominant approach. Surgical management is the primary treatment for the structural coma, while the metabolic coma requires predominantly medical treatment. The diagnosis and management of unconscious patients require extensive clinical assessment, consisting of a careful approach to history-taking and general medical and neurological examinations. Following immediate resuscitation by the ABCDE approach and proper management protocols, physicians should look for causes of loss of consciousness through clinical evidence and investigations. Appropriate management will help to avoid secondary complications related to the impairment of consciousness. The prognostication of a coma is also varied and primarily depends on its etiology. The algorithm for prognostication in a coma is helpful for poor outcome determinants.

Keywords

Coma; Unconsciousness; Glasgow coma scale; Prognostication

1. Introduction

Consciousness consists of awareness of self and environment [1]. A full function of consciousness (arousal) requires the stimulation of the caudal brainstem reticular activating system (RAS) to the cerebral cortices (Fig. 1, Ref. [2]). The RAS consists of multiple neuronal networks, including the locus coeruleus, raphe nuclei, posterior tuberomammillary hypothalamus, and pedunculopontine tegmentum, linking the brainstem to the cortex [2]. These neuronal networks initiate primarily in the brainstem's reticular formation and ascend through synaptic propagates in the intralaminar nuclei of the thalamus to the cerebral cortex [3]. These compartments and the connections between them must be preserved for consciousness to be maintained [4]. Physicians prefer using standardized terminology to define levels of consciousness with terms, for instance, "alert", "drowsy", "stuporous", or "comatose" to prevent misunderstanding and to improve not only their own but also inter-personal communication. Ambiguous words such as "lethargic" or "obtunded" should be avoided, as they lack precision. Drowsiness simulates light sleep and is characterized by easy arousal and the continuation of alertness for a brief period. Stupor refers to a state of near unresponsiveness that needs strenuous or repeated stimulus to elicit a response. Comatose patients have the appearance of being asleep, failure in responding to external stimuli, incapability in responding to inner needs, and incompetence of interaction with the environ-

ment [5].

Tips and tricks: Levels of consciousness are classified into four levels, from normal status to most severe unconsciousness, these being alert, drowsy, stupor, and coma, respectively

2. Causes of unconsciousness

Lesions in the brain that are the leading causes of comatose conditions can be divided into three major types of pathology. The first is widespread dysfunction in both cerebral cortices from ischemia, trauma or inflammation/infection, etc. The second is suppressing cortical function by extrinsic agents, toxins, hypoxia, or internal metabolic derangements such as hypoglycemia, azotemia, hepatic failure, or hypercalcemia. The third is any brainstem lesions that cause impairment to the RAS from either primary upper brainstem lesions or secondary lesions from hemispheres [6–8]. The leading causes of coma are shown in Fig. 2 (Ref. [9]).

Tips and tricks: Bilateral hemispheric dysfunction and impairment of RAS lead to alteration of consciousness.

The causes of unconsciousness may be categorized into two groups based upon treatment subtypes. The causes of structural or surgical coma which may require surgery for treatment include trauma (subdural/epidural damage, diffuse axonal injury, brain contusions, and penetrating brain injury); intracranial hemorrhage (subarachnoid hemorrhage, intracere-

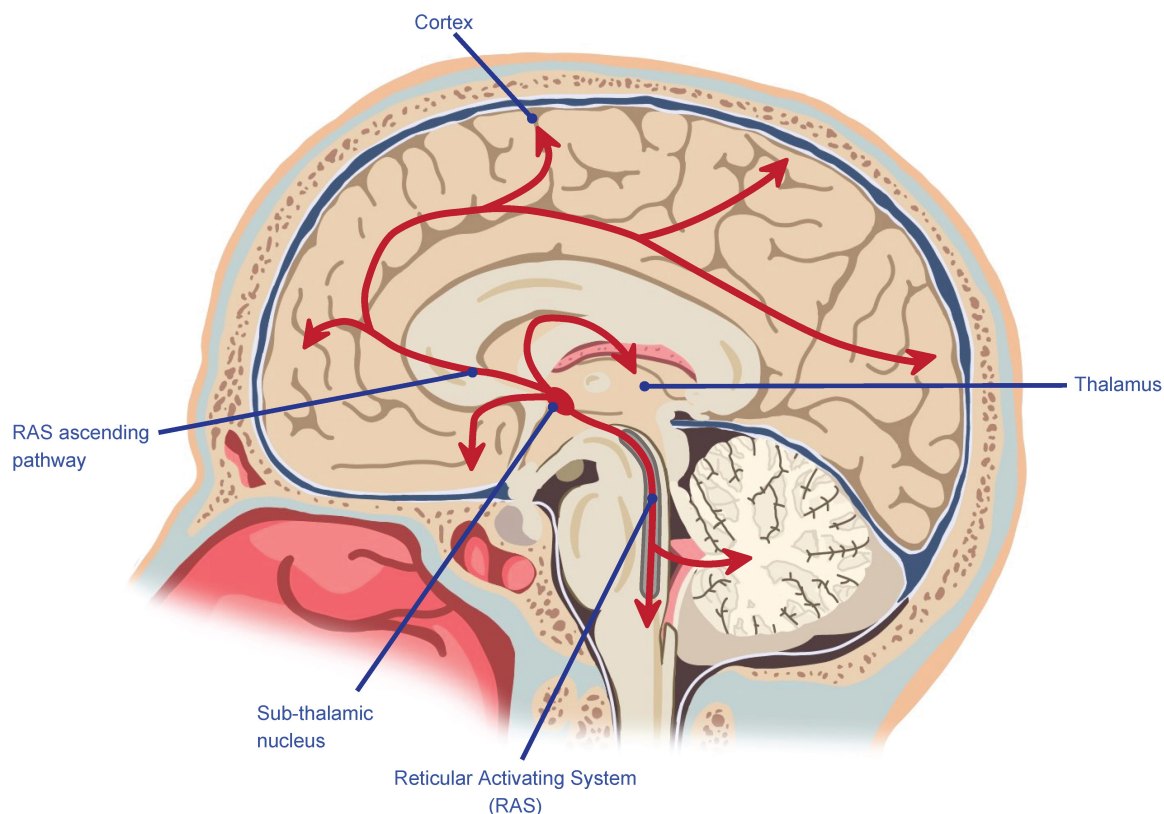


FIGURE 1. Reticular activating system (adapted from Arguinchona *et al.* [2]).

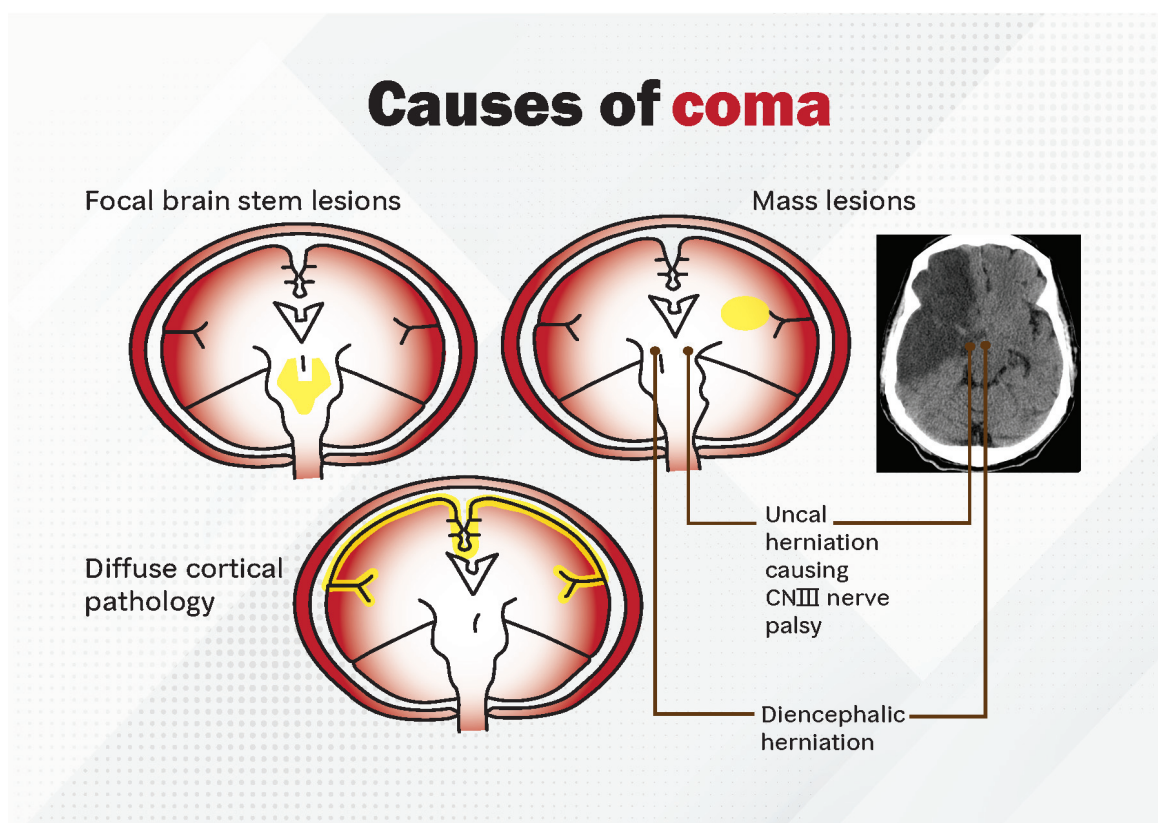


FIGURE 2. The leading causes of coma (adapted from Bates, D.) [9].

bral hemorrhage in posterior fossa e.g., cerebellum or pons or supratentorial parenchymas e.g., putamen, thalamus or lobar location); ischemic stroke involving a large volume of a hemi-

sphere, such as malignant middle cerebral artery infarct with brain herniation; or those affecting the RAS system, such as the so-called tip of basilar artery syndrome with bilateral infarct

of thalami and rostral midbrain; diffuse microvascular disease (thrombotic thrombocytopenic purpura or TTP, scrub typhus and cerebral malaria); tumor (glioblastoma multiforme leading to brain herniation and multiple metastatic brain lesions); and lastly, uncommon disorders such as osmotic demyelination syndrome.

The causes of metabolic or medical unconsciousness that usually require predominantly nonsurgical treatment include drug overdoses (especially benzodiazepines, barbiturates, opioids, and tricyclic antidepressants), infectious diseases (septicemia, bacterial meningoencephalitis, and viral encephalitis), endocrine disorders (hypoglycemia, diabetic ketoacidosis, hyperosmolar coma, myxedema, and hyperthyroidism), metabolic derangements (hyponatremia, hypernatremia, uremia, hepatic encephalopathy, hypertensive encephalopathy, and hypomagnesemic pseudo-coma), toxic reactions (carbon monoxide intoxication, alcohol intoxication, acetaminophen overdoses, and ethylene glycol intoxication), adverse reactions from medication (Reye's syndrome, neuroleptic malignant syndrome, central anticholinergic syndrome, serotonin syndrome, and isoniazid intoxication), deficiency states (thiamine deficiency, particularly Wernicke's encephalopathy, and niacin deficiency syndrome, particularly pellagra), pathologic hypothermia, and psychogenic coma (conversion disorder, depression, and catatonia) [10–13]. The causes of unconsciousness are shown in Table 1.

Tips and tricks: Surgery is a potential treatment for patients with structural coma subtypes, while nonsurgical treatment plays a significant role for patients with metabolic subtypes.

Most studies prefer to initially divide the causes of coma into traumatic and nontraumatic subtypes for more precise prognostication and appropriate treatment [14]. Due to the variety of the causes in nontraumatic subtypes, looking for potentially treatable causes is highly recommended [15]. Traumatic brain injury (TBI) is the most common cause of coma in children [16]. Even under the advanced anti-infective treatment era, central nervous system (CNS) infection remains the most common cause of nontraumatic coma in children during the last two decades [17, 18]. In comparison, hypoxic-ischemic encephalopathy (HIE) and stroke are the most common cause of nontraumatic coma in adults [14, 19, 20].

3. Approaches to treating unconscious patients

3.1 Initial assessment

It is mandatory to quickly confirm that the patient's airway is clear and that the patient is not in shock. If respiration becomes shallow or struggling or there is threat of aspiration with emesis, tracheal intubation should be immediately performed. In contrast, an oropharyngeal airway is adequate for one who breaths normally. If hypotension occurs, a central venous line with intravenous fluids with or without vasopressor agents must be initiated. Oxygen saturation must be kept above 94 percent. Empiric treatment of reversible causes in adults includes 100 milligrams of intravenous thiamine followed by 50 milliliters of intravenous 50% glucose and approximately 0.4 milligrams of intravenous naloxone. Intravenous flumaze-

nil, between 1 to 10 mg, may be helpful if a benzodiazepine overdose is suspected. If seizures develop, they must be monitored and controlled. Emergent metabolic disturbances, e.g., hypoglycemia and extreme hypo- or hyper- kalemia, must also be managed. In patients with elevated intracranial pressure (ICP), lowering the ICP may be sufficient to awaken the patients immediately [10, 19].

Tips and tricks: Three requirements for rescue treatments remain a priority for the initial assessment of unconscious patients. The ABC steps for emergency assessment include clearing airways (A), breathing maintenance (B), and sustaining circulation (C).

3.2 Essential factors in the clinical examination of unconscious patients

3.2.1 History taking

The history-taking of unconscious patients will often be limited. Useful sources of further history may be relatives, friends, or witnesses, if available. The details of the present illness should include the onset of unconsciousness (sudden or gradual), recent complaints (headaches, depression, focal weakness, or vertigo), recent injuries, underlying medical illnesses (diabetes, uremia, or heart disease), and possible exposure to drugs (sedatives or psychotropic drugs) [21, 22].

Tips and tricks: Informative history-taking is crucial for the management of unconscious patients.

3.2.2 General physical examination

Checking vital signs is essential in determining the causes of unconsciousness. Evidence of trauma leads to suspicions of traumatic brain injury. Signs of an acute or chronic systemic illness may be related to metabolic coma. Evidence of drug ingestion, such as needle marks or alcoholic breath, points to drug intoxication. Examinations for nuchal rigidity should not be performed unless neck damage has been excluded [23].

If a slow heart rate appears, any heart block may be suspected. Slow pulse with irregular breathing and high blood pressure suggests an elevated ICP (Cushing's Triad). Hypotension suggests shock. The subtypes of shock may include (1) hypovolemic shock from internal hemorrhage, (2) cardiogenic shock from myocardial infarction, and (3) vasodilatory subtypes from sepsis, intoxication by alcohol, or barbiturates and Addison's disease [24]. Markedly high blood pressure suggests hypertensive encephalopathy, Posterior Reversible Encephalopathy Syndrome (PRES), elevated ICP, or a massive intracranial hemorrhage [23].

Fever should be considered as evidence of infection until proven otherwise. Extremely high body temperature with dry skin is usually associated with heat stroke or intoxication by anticholinergic drugs. Pathologic hypothermia suggests circulatory failure, intoxication by barbiturates or alcohol, myxedema, exposure to cold, or drowning [22].

The odor of breath may also be helpful for a diagnosis. Cyanide poisoning produces a burnt or bitter almond odor [25]. Diabetic patients with a rotten fruit smell suggest ketoacidosis (DKA) [26]. The presence of alcohol is usually easy to smell from the breath [27]. Encephalopathic patients with a musty

TABLE 1. The causes of coma.

Structural or surgical coma	Metabolic or medical coma
Trauma:	
Drug overdose:	
- Subdural damage	- Benzodiazepines
- Epidural damage	- Barbiturates
- Diffuse axonal injury	- Opioids
- Brain contusions	- Tricyclic antidepressants
- Penetrating brain injury	
Intracranial hemorrhage:	Infectious:
- Subarachnoid hemorrhage	- Septicemia
- Intracerebral hemorrhage	- Bacterial meningoencephalitis
Posterior fossa (pontine, cerebellar)	- Encephalitis (e.g., herpes simplex, arboviral infection)
Supratentorial (basal ganglia, lobar)	
Ischemic stroke:	Endocrine disorders:
- Malignant middle cerebral artery infarct with brain edema or pending brain herniation	- Hypoglycemia
Brainstem stroke involving bilateral rostral pons or midbrain	- Diabetic ketoacidosis
- “Top of the basilar” syndrome with bilateral infarct of thalami and rostral midbrain	- Hyperosmolar coma
	- Myxedema
	- Hyperthyroidism
Diffuse microvascular abnormality:	Metabolic abnormalities:
- Thrombotic thrombocytopenic purpura	- Hyponatremia
- Scrub Typhus	- Hypernatremia
- Cerebral malaria	- Uremic encephalopathy
	- Hepatic encephalopathy
	- Hypertensive encephalopathy
	- Hypomagnesemic pseudo-coma
Tumor:	Toxic reactions:
Glioblastoma multiforme with brain herniation	- Carbon monoxide intoxication
Multiple metastatic lesions	- Alcohol intoxication
	- Acetaminophen overdose
	- Ethylene glycol intoxication
Other disorders:	Medication side effects:
Osmotic demyelination syndrome (central pontine myelinolysis)	- Reye’s syndrome
	- Neuroleptic malignant syndrome
	- Central anticholinergic syndrome
	- Serotonin syndrome
	- Isoniazid intoxication
	Deficiency states
	- Thiamine deficiency (Wernicke’s encephalopathy)
	- Niacin deficiency (pellagra)
	Hypothermia
	Psychogenic coma
	- Conversion disorder
	- Depression
	- Catatonia

TABLE 2. The Glasgow Coma Scale.

Component	Scale	Adult	Child <5 years	Child >5 years
Motor	6	Follows commands	Normal spontaneous movements	Follows commands
	5	Localizes pain	Localizes to supraocular pain (>9 months)	Localizes pain
	4	Withdraws to pain	Withdraws from nailbed pressure	Withdraws to pain
	3	Flexion	Flexion to supraocular pain	Flexion
	2	Extension	Extension to supraocular pain	Extension
	1	None	None	None
Verbal	5	Oriented	Age-appropriate speech/vocalizations	Oriented
	4	Confused speech	Less than usual ability; irritable cry	Confused
	3	Inappropriate words	Cries to pain	Inappropriate words
	2	Incomprehensible	Moans to pain	Incomprehensible
	1	None	No response to pain	No response to pain
Eye opening	4	Spontaneous	Spontaneous	Spontaneous
	3	To command	To voice	To voice
	2	To pain	To pain	To pain
	1	None	None	None

Modified from McClintic and Horrall [38].

fetor and urinous smell indicate hepatic and uremic causes, respectively [28, 29]. A strong garlic odor suggests poisoning with arsenic, organophosphates, selenium, or thallium [30].

Also, a careful inspection of the skin and general appearance may be helpful. Bruises or contusions around the head and neck suggest traumatic brain injury. Cerebrospinal fluid (CSF) leakage from the ear or nose and periorbital hemorrhage may be connected to a skull fracture [12]. Profound anemia suggests internal bleeding. Jaundice with signs of liver disease suggests hepatic pre-coma. Cyanosis may be associated with hypoxia [29]. The hemorrhagic macular rash is usually found in meningococcal infections, Staphylococcal septicemia, infective endocarditis, and Rocky Mountain spotted fever [31]. Cherry-red coloration suggests carbon monoxide poisoning [29]. Bullous lesions are found in barbiturate intoxication [12]. Telangiectasia with hyperemia of the face and conjunctivae suggests alcoholism. Puffy face suggests myxedema. Profuse sweating suggests hypoglycemia or shock [29]. Dry skin can be found in cases of diabetic ketosis and uremia [26]. Decreased skin turgor suggests dehydration.

Tips and tricks: Careful physical examination may help uncover clues leading to the diagnosis of the cause of unconsciousness.

3.2.3 Neurological examination

Due to the limitation of communication ability in conscious impairment condition, the examination in comatose patients will adopt a brief version of the neurological examination given to alert patients. The initial goal of the neurological examination is to determine whether it is from a structural cause or a metabolic abnormality, or possibly from both. Two findings that strongly indicate a structural lesion include persistent asymmetrical signs between right and left sides and abnormal reflexes that indicate specific areas within the brainstem [32, 33].

3.2.4 The Glasgow Coma Scale (GCS)

The Glasgow Coma Scale (GCS) was initially created for measuring traumatic brain injuries; however, it has been shown to help determine various degrees of unconsciousness. GCS is also helpful for predictors of outcomes in patients with nontraumatic coma [34]. A scale of 13 to 15 indicates mild unconsciousness. A scale between 9 and 12 indicates moderate unconsciousness, and a scale of 8 or less indicates a severe coma [35–37]. The GCS for adults, small children <5 years old, and children >5 years old is shown in Table 2 (Ref. [38]).

Tips and tricks: The GCS is generally helpful in evaluating consciousness levels in patients with altering degrees of consciousness.

3.2.5 Pupillary response

The pupils become small and symmetrical in metabolic unconsciousness, with an intact light reflex and hippus phenomenon. Unilateral fixed dilated pupil suggests an ipsilateral oculomotor nerve compression due to uncal herniation. Mid-position and non-reacting pupils suggest a midbrain lesion. Pinpoint pupils with poor reaction to light suggest a pontine tegmental lesion. Opiates intoxication leads to pinpoint pupils, while atropine intoxication leads to widely dilated and fixed pupils [39, 40].

Tips and tricks: Pupillary examination is beneficial to determine the localization of the lesions.

3.2.6 Ocular motility

Asymmetric ocular motility accompanies structural rather than metabolic coma. Roving eye movement suggests a light unconsciousness with a diffuse cortical dysfunction of metabolic origin. Lateral and slight downward deviation suggests ipsilateral oculomotor nerve palsy. Medial deviation suggests ipsilateral abducens nerve palsy. The cerebral hemispherical

lesion causes conjugate deviations toward the lesion (“looks at the lesion”), while the unilateral pontine lesion causes conjugate deviation away from the lesion (“looks away from lesion”) [41].

3.2.7 Oculocephalic reflexes (Doll's eye movement)

The intact reaction of oculocephalic reflexes (Doll's eye movement) consists of the deviation of both ocular globes towards the opposite direction of cephalic turning. A fully conscious patient does not have oculocephalic reflex due to voluntary suppression. Once an unconscious patient does not express these symptoms, then a lesion must be located at either the afferent or efferent arm of the reflex loop. The afferent arm includes the labyrinthine complex, vestibular nerve (CN VIII), and neck proprioceptors. The efferent arm includes the oculomotor nerve (CN III), trochlear (CN IV), and abducens nerve (CN VI), and their responsible muscles. If the connective pathways between the afferent and efferent arms in the pons and medulla become interrupted in unconscious patients, the doll's eyes reflex will also be absent. This maneuver should not be performed until cervical spine injury has been excluded to avoid potential damage to the cervical cord [39, 42].

3.2.8 Vestibuloocular reflexes

The irrigating of one tympanic membrane with cold water/saline introduces ipsilateral deviation of both eyes with contralateral fast phase nystagmus lasting for one to two minutes. Conversely, switching to hot water produces the opposite reaction: contralateral deviation, with ipsilateral fast phase nystagmus. Bilateral irrigating with cold water/saline gives rise to a downward deviation with upward nystagmus, and with hot water/saline, the opposite reaction occurs. The absence of any or abnormal responses indicates brainstem dysfunction [43]. Metabolic diseases affecting the brainstem often give rise to loss of vestibulo-ocular and oculo-cephalic responses in their early stages.

In contrast, structural diseases of the brainstem often give rise to abnormal responses, e.g., skew deviation or asymmetrical responses. These tests help predict the outcome of a patient suffering from a brain injury. Abnormal responses imply a poor prognosis, whereas a full range of normal responses implies a good prognosis [29].

Tips and tricks: The presence of oculo-cephalic and vestibulo-ocular reflexes in unconscious patients implies an intact connection between the pons and the midbrain.

3.2.9 Corneal reflex

The corneal reflex indicates the degree of intactness of the pathway from the ophthalmic branch of the fifth cranial nerve through the pons to the seventh cranial nerve and facial muscles [44]. Gently touching the cornea with a thin wisp of sterile cotton will lead to involuntary closure of the ipsilateral eye, as well as the closing of the contralateral eye (consensual response). The corneal reflex usually remains intact until the level of unconsciousness becomes hugely impaired. Bilateral loss of the corneal reflex with light unconsciousness indicates the influence of drugs or local anesthetics in both eyes. The unilateral loss of the corneal reflex indicates a focal neurolog-

ical disease [23, 29].

Tips and tricks: The existence of the corneal reflex in unconscious patients indicates that the lesion is likely located outside the pons.

3.2.10 The motor system

Deep tendon reflexes are reliable, objective signs in the motor system. Muscle tones can be tested by sensing the resistance of the patient's extremities to passive movements. Testing the strength of posturing and local withdrawal reactions is recommended. Local withdrawal reactions may be stimulated by pressing a stick such as a pen or a pencil forcefully against the patient's fingernail, pinching extremities, rubbing the sternum to provoke pain, and watching whether the patient withdraws the corresponding extremity from the pain stimulus. Checking the motor response also has localizing value. Paralyzed extremities will not elicit any response, and the presence of hemiplegia will therefore become evident. Unilateral spontaneous extremity movement indicates a cerebral hemisphere or brainstem lesion. The passive movement of suspected paralyzed extremities falling like a “dead weight” indicates mono or hemiplegia. Asymmetric responses indicate structural lesions, either in the cerebral hemisphere or brainstem. Symmetric responses indicate more diffuse lesions (metabolic encephalopathy). Decorticate responses (adducted arm with flexion at elbow, flexion, and pronation at the wrist, extended at hip and knee) indicate lesions above the level of the red nucleus. Decerebrate responses (arm is extended, adducted, and internally rotated; leg is extended) indicate lesions below the level of the red nucleus but unlikely to be severe metabolic disorders. Complete flaccidity without any response to pain stimuli usually indicates severe CNS depression due to drug overdose [45].

Tips and tricks: Asymmetric motor response in unconscious patients indicates a focal lesion.

3.2.11 Respiratory patterns

Hyperventilation indicates midbrain or upper pons lesions and commonly occurs in metabolic disorders, such as hepatic or uremic encephalopathy, diabetic hyperosmolar, and early stages of generalized elevated ICP. In contrast, hypoventilation indicates a medullary or upper cervical spinal lesion commonly found in drug overdoses and cerebral herniation in its later stages. Cheyne-Stokes respiratory pattern indicates a lesion in the diencephalon commonly found in central transtentorial brain herniation and obstructive hydrocephalus. Ataxic respiration (totally irregular breathing) usually indicates a brainstem dysfunction of a diffuse nature [46].

3.3 Diagnostic studies

It is essential to bear in mind that in order to accurately determine the clinicopathological causes of unconsciousness, the following investigatory scheme can be adopted: In the case of potential focal lesions, the recommended investigations include skull radiographs, computer tomography (CT)/magnetic resonance imaging (MRI) of the brain, ventriculography, electroencephalography (EEG), electrocardiography (ECG), cardiac

monitoring, and carotid/vertebral angiography. In case of potential diffuse lesions, the recommended investigations include an examination of cerebrospinal fluids (CSF), serum glucose, complete blood count (CBC), calcium, sodium, potassium, magnesium, arterial blood gases and pH, liver and renal functions, drug levels, and blood for metabolic panels and blood culture [46].

Tips and tricks: Radiographic studies are crucial in diagnosing patients with potential focal lesions, while laboratory studies remain primary for patients with potential diffuse lesions.

3.4 Management

The ABCDE (A for airway, B for breathing, C for circulation, D for disability, and E for exposure) approach to resuscitation must be applied [47]. The preservation of a clear airway is mandatory. The establishment of a clean airway includes maintaining an initial lateral position, suction to remove secretions, endotracheal intubation, and mechanical ventilation if patients cannot protect against aspiration, hypoxia, or hypoventilation. Arterial blood gas should be evaluated and further monitored by oxygen saturation. If shock is presented, it needs to be managed immediately [48]. An IV line should be established. The level of consciousness should be immediately evaluated. Clothing should be removed to permit evaluation [49]. Blood drawn for glucose, drugs, electrolyte, liver, and renal functions should be considered. Urine samples for glucose and ketone bodies may be helpful. Diagnostically and therapeutically, gastric lavage may also be helpful. If the patient does not immediately recover from unconsciousness, the patient's ongoing requirements must be evaluated. The patient must be transferred to an intensive care unit (ICU) to allow for critical management. Whether the patient is in a critical care facility or the regular ward, the ongoing requirements and priorities remain unchanged [50, 51].

Tips and tricks: ABCDE steps for emergency approach include clearing airways (A), breathing maintenance (B), sustaining circulation (C), assessing disability (D), and ensuring exposure (E).

3.4.1 Respiratory management

Maintaining a patient's airway and promoting adequate ventilation is essential. Dentures must be removed, while loose teeth or crowns must be identified. The early application of a nasogastric tube will allow for the elimination of contents in the stomach, thus lowering the risk of aspiration. Oropharyngeal airways protect the tongue from blocking the airway and offer a passage that allows the patient to inspire. Airways also help to eliminate secretions from the trachea via suctioning. The lateral recumbent position, with the head of the bed slightly raised at about 10 to 30 degrees, is highly recommended. When the threat to the airway is still ongoing and cannot be resolved by positional adjustment and the clearance of secretions, intubation with an endotracheal tube becomes essential to prevent the airway from aspiration and the correlated risk of pulmonary infection. If impairment of consciousness is continued and an artificial airway is still needed, then a tracheostomy must be considered. Physiotherapy encourages pulmonary expansion,

assists the elimination of secretions, and helps in the prevention of many complications. Pulse oximetry helps monitor the use of oxygen administration. Alterations in the respiratory pattern may indicate respiratory failure or impairment of the respiratory control center in the brain [46, 52].

Tips and tricks: Adequate respiration needs to be ensured throughout the course of management.

3.4.2 Cardiovascular management

Quality of pulse, pulse pressure, and heart rate may be important in an unconscious patient with unstable blood pressure. Low blood pressure, together with the presence of tachycardia and a weak pulse on palpation, may indicate hypovolemia. Immobility from unconsciousness can affect cardiovascular functions, with elevated heart workload and central fluid shifting from the lower extremities to the intrathoracic and intracranial space. The venous thromboembolism leading to pulmonary emboli is a well-known life-threatening condition from the effects of immobility. Therefore, the application of pneumatic stockings should be considered in all unconscious patients. Anticoagulants will also lower the risks of venous thromboembolism [53, 54].

Tips and tricks: Pulmonary embolism is a preventable cause of death in unconscious patients.

3.4.3 Nutrition and hydration

Monitoring electrolyte and metabolic status are essential. Serum pre-albumin is the most reliable test for protein nutritional status evaluation [55]. Immobilization in unconsciousness also leads to insulin dysfunction. An intravenous insulin sliding scale may be needed to control blood glucose levels within 140 to 180 mg/dL. The most common recommended method for feeding during the early period of unconsciousness is a nasogastric tube. Cooperation with dietitians will assist in assessing and planning the patient's nutritional needs [45, 56].

Tips and tricks: Feeding should not be delayed in unconscious patients.

3.4.4 Gastrointestinal management

Loose stool can be a result of poorly tolerated enteral feeding. Laxatives are usually required to assist in the evacuation of the feces. Monitoring bowel functions with the use of a chart should help to evaluate the need for the treatment. Rectal preparations, such as suppositories and enemas, may be sometimes helpful. Manual evacuation is an invasive intervention but is sometimes necessary [57].

3.4.5 Genitourinary management

An unconscious patient usually becomes urinary incontinent. If overflow incontinence is evident or maintaining fluid input/output balance is necessary, a urinary catheter should be considered to eliminate urine [58].

3.4.6 Hygiene needs and skin care

Skin ulcers usually occur in an unconscious patient due to continuous pressure from immobilization. Correct body positioning, frequent turning, and the application of a pressure-relieving mattress will lower these risks. Incontinence, mois-

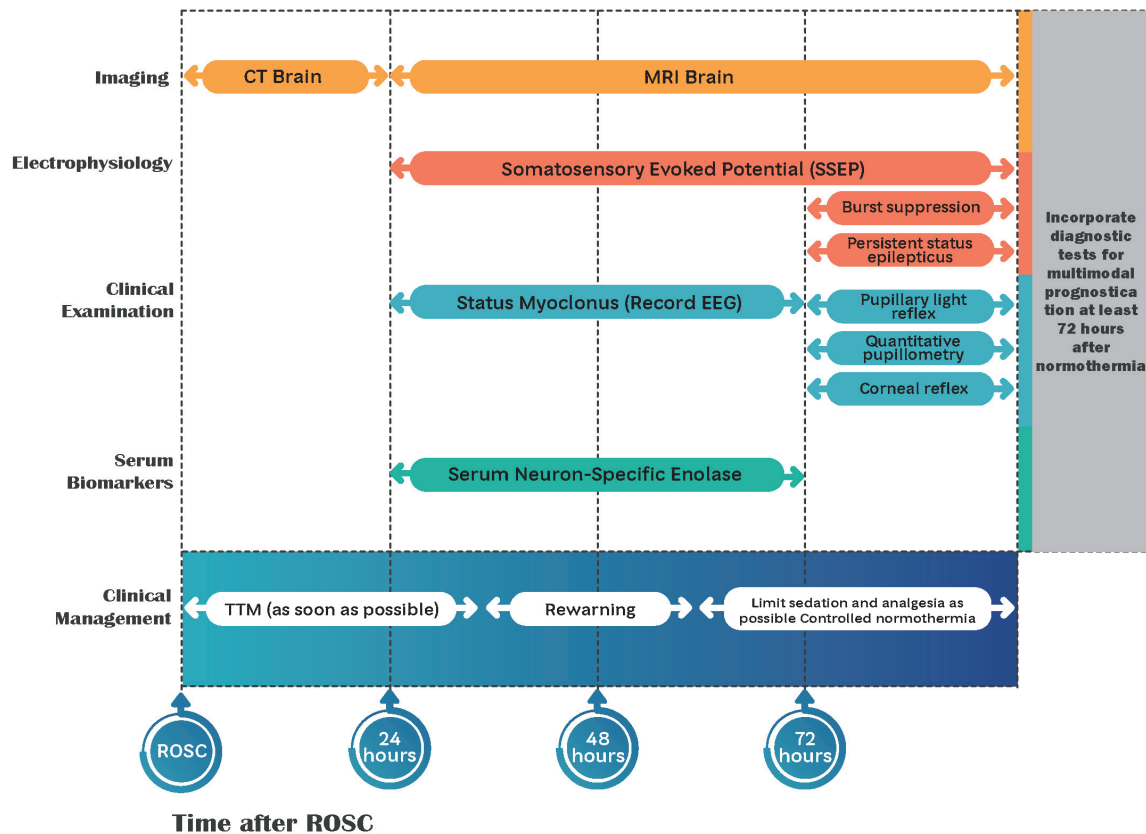


FIGURE 3. The algorithm for prognostication in post-cardiac arrest patients treated with TTM (modified from Panchal *et al.* [64]).

ture, poor nutritional status, obesity, and the elderly contribute to decubitus ulcer formation. Therefore, a pressure area assessment tool, the Waterlow scale, should be applied to identify risks [59]. In evaluating the eyes, watch for signs of inflammation, corneal drying, abrasions, and edema. Gentle cleaning with soft gauze and isotonic sodium chloride should be sufficient. Artificial tears may also be applied as drops or gel to help moisten the cornea and sclerae. Gentle cleaning of the nasal cavity with gauze and water or saline is recommended. Gauze and water or saline can also be used to clean around the ear canal [60].

Tips and tricks: The patients' bowels, bladder, hygiene, and skin care should not be ignored.

4. Prognostication

Invented by the American Academy of Neurology in 2006, the algorithm for prognostication in patients with coma after restoring spontaneous circulation from cardiac arrest has become a landmark guideline [61]. The primary purpose of the algorithm is to determine the poor outcomes for withdrawal of life-sustaining treatment, although most post-cardiac arrest patients fall into indeterminate outcomes. However, due to improved outcomes with targeted temperature management (TTM), clinical and surrogate markers in the algorithm need to be interpreted more carefully in patients treated with TTM [62, 63]. The recent resuscitation guidelines updated the algorithm using multimodal evaluation (as shown in Fig. 3, Ref. [64]) to ensure better accuracy in determining the prognosis in post-

cardiac arrest patients treated with TTM [64]. While a tool for prognostication in post-cardiac arrest patients is available [65], such a tool in coma patients outside post-cardiac arrest is much less established [66]. In general, for patients who remain comatose for more than four weeks, the chance of meaningful recovery is low. Therefore, future studies should focus on innovative tools or techniques to better predict outcomes in various types of patients with impairment of consciousness [67, 68].

Tips and tricks: Targeted temperature management is an essential, acute treatment that may improve outcomes in conscious-impairment patients after cardiac arrest.

The state of coma from any causes is usually temporary; subsequently, patients may demonstrate partial or full recovery after days or weeks or even months, or may develop brain death. Patients with minimal recovery acquire a vegetative state. Patients in a vegetative state other than unresponsiveness should be able to maintain their circadian rhythm, respiration, digestion, or thermoregulation. Recently, unresponsive wakefulness syndrome has been proposed as a substitute for persistent vegetative state [69]. Patients in unresponsive wakefulness syndrome regain spontaneous eye-opening but show no evidence of awareness of self or environment. Simple reflexes, e.g., yawning, grinding teeth, and spastic limbs, can be found in patients with unresponsive wakefulness syndrome. The state of unresponsive wakefulness syndrome can be temporary, prolonged, or permanent. Patients who regain some consciousness acquire a minimally conscious state [70]. Language processing is a criterion used to divide the minimally

conscious state into plus and minus subtypes. A patient with a minimally conscious state *minus* demonstrates intact pursuit eye movements, localization to pain stimuli, and spontaneous motor response.

In contrast, a patient with a minimally conscious state *plus* can follow simple commands and communicate intentionally but not functionally [71, 72]. The minimally conscious state may also be transitory, prolonged, or persistent. A patient who regains more consciousness may improve from a minimally conscious state but usually experiences significant cognitive and motor deficits [70]. Several scoring systems have been developed to measure pain and neurobehavioral function in unresponsive patients; however, these have not been widely used in routine clinical practice [73, 74].

Tips and tricks: A coma patient may still progress toward unresponsive wakefulness syndrome, minimally conscious state or functional recovery.

Amantadine is the only pharmacologic therapy that shows some clinical benefits in unresponsive patients after traumatic brain injury [75, 76]. However, no clinical trials support the clinical benefit of Amantadine in unconscious patients outside traumatic brain injury [77]. At the same time, transcranial direct current stimulation is the only non-pharmacologic therapy that shows some clinical benefits in patients with a minimally conscious state [76, 77]. However, routine use of Amantadine or transcranial direct current stimulation remains off-labeled due to lack of randomized control trials [77].

5. Summary

The pathways of consciousness in the brain are well established. Lesions affecting the pathways can lead to impairment of consciousness. The etiologies of unconsciousness can be classified into the structural/surgical and metabolic/medical subtypes. Although there are several limitations in obtaining clinical data from unconscious patients, history taking, general and neurological examinations, and diagnostic studies are the keys to accurate diagnosis of related causes. Holistic management, including a resuscitation approach for life-saving, followed by systemic management to prevent secondary complications, is recommended. The prognosis of coma patients depends on the degree of permanent brain injury from any causes.

AUTHOR CONTRIBUTIONS

SM contributed to conception and design of the work, data collection, drafting the article, critical revision of the article, final approval; WS contributed to data collection, drafting the article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Sombat Muengtawepongsa is serving as one of the Guest editors of this journal. We declare that Sombat Muengtawepongsa had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to FL.

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