Management of the Patient with Diminished Responsiveness

Sara Hocker, MD[a],*, Alejandro A. Rabinstein, MD[b]

KEYWORDS

• Coma • Encephalopathy • Management • Prognosis

Coma is an alteration of consciousness in which a person appears to be asleep, cannot be aroused, and has no evidence of awareness of the environment. Management of coma requires an organized and timely approach to determine the likely cause and initiate treatment. Coma often represents as a medical or surgical emergency that requires immediate action to preserve life or neurologic function. Examples include intoxications; acute metabolic derangements, such as diabetic ketoacidosis and fulminant hepatic failure; central nervous system (CNS) infections; basilar artery thrombosis; nonconvulsive status epilepticus; and acute cerebral mass lesions, such as intracerebral hemorrhage (**Fig. 1**) or large vessel territory ischemic stroke.

This article summarizes the main priorities in the acute treatment of comatose patients. A separate section addresses important factors in the long-term care of patients who remain in a prolonged state of unconsciousness and outcome prediction in patients who fail to awaken in the first days to early weeks. The evaluation and differential diagnosis of severe encephalopathy and coma are reviewed in a previous issue of *Neurologic Clinics*.

EMERGENCY MANAGEMENT

Coma is a neurologic emergency until proved otherwise. Evaluation and early intervention should proceed promptly and simultaneously. An organized protocol for urgent triage, evaluation, and management of coma is recommended (**Box 1**).

Management of the airway, ventilation, circulation, and sedation in patients with suspected or known neurologic injury requires understanding of the underlying issues

Fig. 1. An axial cut CT scan of the brain at the level of the temporal horns showing extensive subarachnoid hemorrhage and intraparenchymal hemorrhage within and extending through the dorsal pons into the fourth ventricle, with large amounts of blood also in the third and lateral ventricles, resulting from rupture of a distal basilar artery aneurysm. There is also obstructive hydrocephalus with dilation of the ventricles.

of elevated ICP, cerebral perfusion, neuromuscular status, and anatomy of the neuraxis.

Intubation is indicated in patients with hypoxia (SpO_2 <90%), hypoventilation or an inefficient respiratory pattern (ie, irregular or gasping), risk of aspiration as assessed by patient's ability to spontaneously swallow or swallow in response to suctioning, or anticipated deterioration. Cheyne-Stokes breathing and central neurogenic hyperventilation are not necessarily incompatible with normal gas exchange.

If patients are able to communicate verbally, the airway is not likely immediately jeopardized; however, patients presenting with alteration in the content or level of consciousness require repeated assessment of airway patency. A Glasgow Coma Scale score of 8 or less or the presence of nonpurposeful motor responses in a patient who has sustained head injury strongly suggests the need to establish a definitive airway.

If trauma is suspected, standard of care dictates that the cervical spine should be stabilized with a collar while securing the airway. If immobilization devices must be removed temporarily, direct laryngoscopy with manual in-line stabilization is standard of care for acute trauma patients with suspected cervical spine injury. The procedure was adopted because of weak empirical data and expert opinion; however, more recent data indicate that direct laryngoscopy and intubation are unlikely to cause clinically significant movement, may not immobilize injured segments, and degrade laryngoscopic view, which may cause hypoxia and worsen outcomes in traumatic brain injury.[1] It can be assumed that this may occur in any acutely brain-injured patient.

In cases of suspected elevated ICP, rapid sequence intubation is the preferred method of securing the airway because it provides protection against the reflex responses to laryngoscopy and resultant elevations in ICP. These reflexes occur

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Box 1
Emergent management of coma in adults

Initial stabilization

Intubate if airway patency is compromised, gas exchange is inadequate, or respiratory pattern is inefficient.

Supplement oxygen.

Ensure adequate intravenous (IV) access.

Assess blood pressure and treat as indicated by the situation.

Obtain 12-lead ECG and initiate continuous cardiac monitoring.

Stabilize cervical spine if trauma suspected.

Treat witnessed seizures with lorazepam (2-4 mg IV), repeating every 5 minutes up to 8–16 mg depending on patient weight. Load with 20-mg/kg phenytoin equivalent fosphenytoin IV while administering the second or third dose of lorazepam.[20]

Initiate therapeutic hypothermia if postcardiac resuscitation encephalopathy is present.

Empiric interventions

Thiamine, 100 mg IV

Dextrose, 50% solution, 50 mL IV (after thiamine)

If ingestion is suspected, administer naloxone, 0.4–2 mg IV (may repeat in 2–3 minutes if inadequate response).

For suspected increased intracranial pressure (ICP), simultaneously hyperventilate and administer 1–2 g/kg IV 25% mannitol (or 30 mL 23% saline if central access is available) while obtaining a noncontrast CT scan of the head to determine if neurosurgical consultation is indicated

If infection is suspected, obtain blood cultures and administer dexamethasone and broad-spectrum antibiotics (third-generation cephalosporin, vancomycin, ampicillin, and acyclovir) while obtaining CT scan and lumbar puncture.

For suspected nonconvulsive SE, obtain emergent electroencephalogram. If suspicion is strong, start empiric treatment with lorazepam and fosphenytoin.

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even in comatose patients without appropriate use of pretreatment and induction agents. The choice of medications is dependent on a patient's preintubation blood pressure (**Table 1**).

Once the airway is secured, oxygen saturation should be measured and supplemental oxygen provided. Adequacy of ventilation should be assessed by examination and arterial blood gases. Moderate hyperventilation (target $Paco_2$ 30–35 mm Hg) to lower ICP should be reserved for patients with increased ICP and considered a bridge therapy until osmotherapy can be administered or invasive treatment (such as placement of an external ventricular drain, in the case of obstructive hydrocephalus or hemicraniectomy, or suboccipital decompression, in the case of supratentorial or infratentorial mass lesions) can be performed. Routine hyperventilation may exacerbate cerebral ischemia by inducing cerebral vasoconstriction.

Appropriate IV access should be established with at least 2 large bore IVs and placement of a central line or intraosseous access if vasopressors are necessary.

All patients presenting with coma should receive thiamine and glucose without waiting for laboratory results or gathering of social history to treat potential hypoglycemia and avoid precipitating Wernicke encephalopathy. Although the use of a coma

Table 1	
Pretreatment and induction agents in the neurologically injured patient	
Normotensive or Hypertensive	**Hypotensive**
Intubation minus 3 minutes • Lidocaine, 1.5 mg/kg • Fentanyl, 2–3 –g/kg, to attenuate the reflex sympathetic response to intubation	Intubation minus 3 minutes • Fluids • Blood products • Inotropes • Pressors to maintain MAP >65 mm Hg
At time of intubation • Etomidate, 0.3 mg/kg, or propofol, 1.5 mg/kg • Succinylcholine,[a] 1.5 mg/kg, or rocuronium, 1.2 mg/kg	At time of intubation • Etomidate, 0.3 mg/kg, or ketamine, 0.5–1 mg/kg • Succinylcholine,[a] 1.5 mg/kg, or rocuronium, 1.2 mg/kg

[a] Succinylcholine should be avoided in patients who are very rigid because of the risk of inducing severe hyperkalemia.

cocktail, consisting of glucose, thiamine, naloxone, and flumazenil, is used frequently in patients presenting with an acute alteration of consciousness, a systemic review of trials considering outcome and adverse effects suggested that it is reasonable to use glucose and thiamine in all patients but that treatment with naloxone and flumazenil should be used only in the setting of known or strongly suspected drug overdose.[2] All comatose patients should have a baseline 12-lead ECG and have their cardiac rhythm monitored continuously for potentially life-threatening arrhythmias. Any witnessed seizures or signs of intracranial hypertension (ie, herniation syndrome is evident clinically or seems imminent based on CT findings) should be treated immediately (see **Box 1**). If patients have just undergone cardiopulmonary resuscitation after a witnessed ventricular fibrillation or ventricular tachycardia arrest, hypothermia should be initiated immediately while obtaining cardiology consultation.[3] Most hospitals now have protocols in place for therapeutic hypothermia after cardiac arrest. If there is no obvious cause for coma, a search should begin for historical or clinical findings. When a diagnosis is suspected, empiric treatments can be implemented while further diagnostic evaluation takes place (see **Box 1**).

PRINCIPLES OF SUPPORTIVE CARE—PREVENTING SECONDARY INJURY

Limiting secondary brain injury must be a priority in the initial management of coma because any additional insult in an acutely brain-injured patient directly worsens outcome and decreases the potential for functional recovery. Outcomes in patients with intracranial catastrophes are related to the ability to maintain cerebral oxygenation and perfusion, beginning with the initial evaluation in the field.[4]

Secondary injury can result from hypoxemia, hypotension, hyperthermia, or metabolic derangements. Hypoxia must be aggressively corrected; however, excessive oxygen supplementation may also worsen outcomes.[5,6] Hypercarbia should also be avoided because it can worsen intracranial hypertension.

Fluid resuscitation with isotonic solutions and, in refractory cases, infusion of vasopressors are indicated when systolic blood pressure is less than 90 mm Hg. Cerebral perfusion pressure, calculated by subtracting mean arterial pressure (MAP) from ICP, should remain above 60 mm Hg[7] in patients with ICP monitoring. In practice, however, the majority of comatose patients do not require ICP monitoring and in these patients the focus is should be on maintaining an adequate systemic blood pressure.

Extreme hypertension (MAP above 140 mm Hg) should be corrected with 10 mg IV labetalol, 10 mg IV hydralazine, or continuous infusion of IV nicardipine (starting at 5 mg/h). Sodium nitroprusside should be administered in refractory cases. It is prudent to withhold antihypertensive therapy in patients with less severe hypertension until the cause is known and further information is obtained because acutely lowering the blood pressure may compromise cerebral perfusion when intracranial hypertension is present.

For suspected or known elevation of ICP, pain and agitation should be treated with short-acting agents, hyperthermia and severe metabolic derangements should be corrected, and the head of the bed should be maintained at or above 30°.

MANAGEMENT OF SPECIFIC CAUSES OF COMA

After securing the airway, ensuring adequate ventilation and circulation, enacting appropriate measures of supportive care, and initiating empiric treatments based on available history and clinical signs, diagnostic evaluation may reveal a specific cause of coma. The following are generally accepted measures for treatable causes of coma not already addressed with emergency management:

- Correct severe hyponatremia with 3% hypertonic saline after placing a central venous catheter.
- Hypercalcemia may be treated with saline rehydration infusion followed by parenteral bisphosphonate pamidronate.
- Use available antidotes and consider hemodialysis for known ingestions.
- Aggressively hydrate patients with nonketotic hyperosmolality.
- Provide hydration and insulin for patients with diabetic ketoacidosis.
- Dialyze patients with acute renal failure.
- Administer corticosteroids for addisonian crisis.
- Give antithyroid drugs and β-blockers for thyrotoxicosis.
- Replace thyroid hormone for myxedema coma.
- Administer lactulose for acute liver failure or portosystemic encephalopathy.
- Give corticosteroids and obtain neurosurgical consultation for pituitary apoplexy.
- IV and/or intraarterial thrombolysis with or without mechanical thrombectomy may be instituted for acute basilar or carotid artery thrombosis (**Fig. 2**).
- Vasodilators should be given for hypertensive encephalopathy, but precipitous drop in blood pressure should be avoided.
- Treat cerebral venous and dural sinus thrombosis with heparin.
- Treat hydrocephalus with ventricular drainage.
- Mass lesions with signs of impending herniation should be treated with osmotherapy, corticosteroids (if vasogenic edema), hyperventilation, surgical resection, evacuation, or decompression.

LONG-TERM MANAGEMENT

Comatose patients may regain consciousness, remain unconscious, or lose all brain function (brain death). Most awaken within the first 2 weeks. Those who awaken may remain in a minimally conscious state (MCS) or in a persistent vegetative state (PVS) or they may become fully conscious but disabled or experience a complete recovery.

Treatment of patients in these categories is generally supportive and aimed at preventing complications related to chronic illness. Supportive care in the chronic critically ill may include tracheostomy, percutaneous gastrostomy, and bowel and
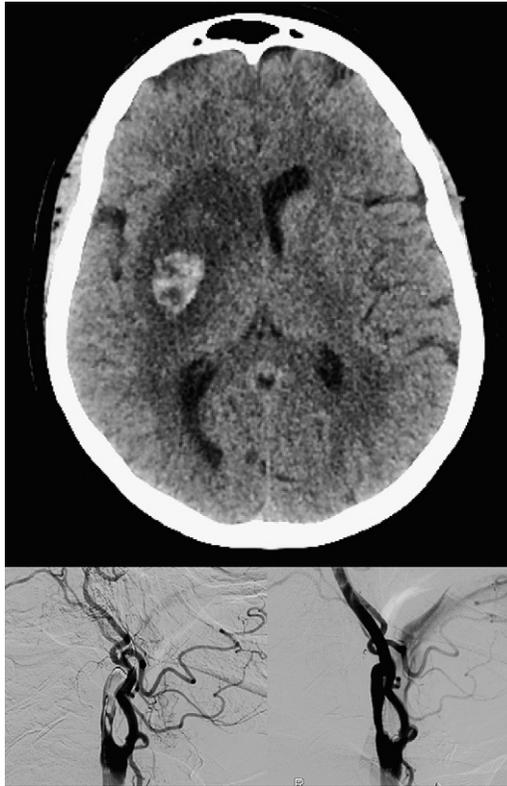
Fig. 2. (*Top*) Noncontrast CT scan showing hemorrhagic transformation of a striatocapsular infarct after revascularization of a right internal carotid artery occlusion through an endovascular procedure with Merci and Penumbra devices. (*Bottom left*) Diagnostic angiography with selective catheterization of the right internal carotid artery showing high-grade stenosis. (*Bottom right*) Right internal carotid artery post mechanical thrombectomy and stenting.

bladder care. Patients may be liberated from the ventilator and have their tracheostomy removed later if secretions are not a problem. Infection surveillance is important because colonization and infection with resistant bacteria are not uncommon. Although methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) may be reduced by strict isolation, meticulous hand hygiene by health care providers, and avoidance of multiple antibiotics, a recent large cluster-randomized trial found that surveillance for MRSA and VRE colonization and the expanded use of barrier precautions were not effective in reducing the transmission of MRSA or VRE, although the use of barrier precautions by providers was less than what was required.[8] Deep venous thrombosis prophylaxis is important in this population although thrombosis is less common in the chronic than in the acute phase of critical illness. Other complications in the long-term management of patients with impaired consciousness include contractures and decubitus skin ulcers. Contractures can be reduced by physical therapy. Decubitus skin breaks and ulcers can be prevented by special beds and monitoring of pressure sites along with frequent turning.

Neurostimulation is unproved in MCS and shown of no benefit in PVS. Dopaminergic agents, such as bromocriptine, zolpidem, and lamotrigine, are commonly

used stimulant drugs in MCS but have not proved beneficial. Amantadine, a dopaminergic agonist and N-methyl-D-aspartic acid antagonist, was recently shown to improve both clinical signs of increased consciousness and functional behaviors during 4 weeks of treatment compared with placebo in a study presented at the 63rd annual meeting of the American Academy of Neurology.[9]

OUTCOME PREDICTION

Outcome prediction in acutely comatose patients is primarily influenced by the underlying cause and the degree of primary and secondary brain injury. To a lesser degree, outcome might be affected by physician expectation. When, in a physician's judgment, aggressive care would be futile and life-support measures are withdrawn, leading to death, this sequence of events could represent a self-fulfilling prophesy.[10] The true impact of this possibility in clinical practice is not known because most of the studies on predictors of poor outcome after acute brain insults have not taken into full account the potential influence of withdrawal of life-support measures. Therefore, it is prudent to acknowledge the limitations of prognostic models when discussing with families the possible outcome of a patient.[11]

Daily clinical examination is the most valuable prognostic tool. Confounding factors, such as sedatives and paralytic drugs, should be avoided to the extent possible to allow for careful examination.

Outcome after anoxic-ischemic brain injury in patients who have not been treated with therapeutic hypothermia is well studied. Four factors that predict poor outcome in this population include (1) absent pupillary light reflex, corneal reflexes, or motor responses at day 3, (2) absent somatosensory evoked potential cortical responses, (3) myoclonic status epilepticus, and (4) increased neuron-specific enolase (<33 ng/mL) at any time during the first 3 days. Current studies evaluating the validity of these factors in the hypothermia treated population are conflicting[12,13] and further research is needed in this area.

Outcome in CNS infections is affected by time to administration of antibiotic or antiviral drugs and corticosteroids.[14,15] With timely adequate antimicrobial and supportive therapy, prognosis can be favorable.

Outcome after traumatic brain injury is difficult to predict. Many young patients make a good recovery despite severe CT scan abnormalities and slow progress. Traumatic brain injury is a leading cause of death and disability worldwide, with most cases occurring in low-income to middle-income countries. Prognostic models, such as those developed from the Corticosteroid Randomization After Significant Head Injury trial[16] and the International Mission for Prognosis and Analysis of Clinical Trials in TBI database,[17] may improve predictions of outcome and help in clinical research. These prognostic models, which include simple variables, are available on the Internet (http://www.crash.lshtm.ac.uk/). The strongest predictors of outcome are age, motor score, pupillary reactivity, and CT characteristics, including the presence of traumatic subarachnoid hemorrhage.[18]

Surgery is no better than medical management in deep ganglionic hemorrhage but evacuation of cerebellar hematoma can result in dramatic improvement. Deteriorating patients with an expanding lobar hematoma may benefit from evacuation[19] but the degree of benefit is uncertain.

Outcome after aneurysmal subarachnoid hemorrhage (aSAH) is determined by initial clinical grade; 50% recover to a better grade and some patients may fully recover. Outcomes in aSAH have improved during the past 3 decades. The chance of a patient surviving an aSAH has increased by 17% during the past 3 decades

and is approximately 65%, whereas incidence has remained stable at 3 per 100,000 patient-years. Two-thirds of aSAH survivors regain functional independence, half have cognitive impairments, half are dissatisfied with life, and only a third resume the same work as before the event.[20,21]

MCS may seem a better outcome for the family than PVS but may be a worse outcome for patients who could potentially have some awareness of devastating injury. Patients in MCS may further recover but no predictors are known.

Patients in PVS for less than 3 years may rarely partially recover, and when they do it is mostly after traumatic brain injury. Nonetheless, all patients remain severely disabled. Patients in PVS for 3 years or more do not recover; they have remarkable generalized brain atrophy on CT scan.

SUMMARY

- Acute coma must be considered a neurologic emergency.
- An organized protocol for urgent triage, evaluation, and management of coma is strongly recommended.
- The main priority after securing the airway and ensuring adequate ventilation and circulation is the limitation of secondary brain injury.
- The first priority with an acute structural cause of coma is treatment of increased ICP.
- The first priorities with a possible CNS infection are broad antibiotic and antiviral coverage and corticosteroids.
- Tracheostomy, percutaneous gastrostomy, bladder and bowel care, infection surveillance, and deep venous thrombosis prophylaxis are key components of longer-term care.
- The prognosis for neurologic recovery depends largely on cause and ranges from good prognosis for uncomplicated drug intoxications to poor prognosis for severe hypoxic ischemic injury.
- Outcome may be influenced by physician expectation.

REFERENCES

1. Manoach S, Paladino L. Manual in-line stabilization for acute airway management of suspected cervical spine injury: historical review and current questions. Ann Emerg Med 2007;50(3):236–45.
2. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. JAMA 1995;274(7):562–9.
3. Chamorro C, Borrallo JM, Romera MA, et al. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. Anesth Analg 2010;110(5):1328–35.
4. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216–22.
5. Davis DP, Meade W, Sise MJ, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma 2009;26(12):2217–23.
6. Kilgannon JH, Jones AE, Shapiro NI, et al, Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 2010;303(21):2165–71.
7. Dandapani BK, Suzuki S, Kelley RE, et al. Relation between blood pressure and outcome in intracerebral hemorrhage. Stroke 1995;26:21–4.

8. Huskins WC, Huckabee CM, O'Grady NP, et al. STAR*ICU Trial Investigators. Intervention to reduce transmission of resistant bacteria in intensive care. N Engl J Med 2011;364(15):1407–18.

9. Katz D, et al. The effectiveness of amantadine hydrochloride in improving level of consciousness and functional recovery in patients in the vegetative or minimally conscious state after traumatic brain injury [abstract]. Plenary session: contemporary clinical issues and case studies—63rd Annual Meeting of the American Academy of Neurology. April 9–16, Honolulu, Hawaii, 2011.

10. Becker KJ, Baxter AB, Cohen WA, et al. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology 2001;56(6):766–72.

11. Rabinstein AA. Ethical dilemmas in the neurologic ICU: withdrawing life-support measures after devastating brain injury. Continuum 2009;15(3):13–25.

12. Bisschops LL, van Alfen N, Bons S, et al. Predictors of poor neurologic outcome in patients after cardiac arrest treated with hypothermia: a retrospective study. Resuscitation 2011;82(6):696–701.

13. Fugate JE, Wijdicks EF, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol 2010;68(6):907–14.

14. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39(9):1267–84.

15. van de Beek D, de Gans J, McIntyre P, et al. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2007;1:CD004405.

16. Roberts I, CRASH trial management group. The CRASH trial: the first large-scale randomized controlled trial in head injury. Corticosteroid randomization after significant head injury. Natl Med J India 2002;15(2):61–2.

17. Roozenbeek B, Maas AI, Marmarou A, et al. IMPACT Study Group. The influence of enrollment criteria on recruitment and outcome distribution in traumatic brain injury studies: results from the impact study. J Neurotrauma 2009;26(7):1069–75.

18. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med 2008;5(8):e165 [discussion: e165].

19. Rabinstein AA, Atkinson JL, Wijdicks EF. Emergency craniotomy in patients worsening due to expanded cerebral hematoma: to what purpose? Neurology 2002; 58(9):1367–72.

20. Nieuwkamp DJ, Setz LE, Algra A, et al. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. Lancet Neurol 2009;8:635–42.

21. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. Lancet Neurol 2011;10(4):349–56.