The management of coma

Tim Cooksley
Mark Holland

Abstract

Coma is a medical emergency that can challenge the diagnostic and management skills of any clinician. A systematic and logical approach is necessary to make the correct diagnosis, the broad diagnostic categories being neurological, metabolic, diffuse physiological dysfunction and functional. Even when the diagnosis is not immediately clear, appropriate measures to resuscitate, stabilize and support a comatose patient must be rapidly performed. The key components in the assessment and management of a patient, namely history, examination, investigation and treatment, are performed in parallel, not sequentially. Unless the cause of coma is immediately obvious and reversible, help from senior and critical care colleagues is necessary. In particular, senior help is needed to make difficult management decisions in patients with a poor prognosis.

Keywords Acute brain injury; alcohol intoxication; coma; diabetic coma; drug intoxication; metabolic emergencies; neurological emergencies; post-ictal; stroke; unconscious

Key points

- Coma is a time-dependent medical emergency
- The traditional components of patient assessment should be performed in parallel and not sequentially
- Physicians should be familiar with the common causes of coma — neurological, metabolic, physiological brain dysfunction and psychiatric
- Reversible causes of coma are more likely in patients with a normal computed tomography scan of the brain and no focal neurology
- The prognosis of coma is determined by the underlying cause and often cannot be performed accurately in the early stages

Definition

Unconsciousness or coma is defined as a sleep-like state, resulting from a diverse range of aetiologies and pathologies, from which the patient cannot be aroused. The patient is completely unaware of and unresponsive to external stimuli, with the exception of motor responses such as eye opening and/or limb withdrawal to painful stimuli.[1]

Pathophysiology of coma

The pathophysiology of coma is complex. It is caused by two primary mechanisms. The first is a diffuse insult to both cerebral hemispheres. The second is a disruption of the ascending reticular activating system in the midbrain and pons, where signals are carried to the thalamus and cortex. The thalamus plays a crucial role in maintaining arousal. The thalamus and ascending reticular activating system can be damaged either by direct insult or by problems arising within the brainstem.[2]

Differential diagnosis of coma

The most likely diagnoses in an unconscious patient are shown in Table 1. They can be categorized as:

- **neurological** — from structural injury of the cerebral hemispheres, or direct injury to or extrinsic compression of the brainstem
- **metabolic** — usually an acute metabolic or endocrine derangement (e.g. hypoglycaemia)
- **diffuse physiological brain dysfunction** (e.g. intoxication with alcohol, drug overdose, seizures, hypothermia)
- **psychiatric** — a functional as opposed to organic cause. Psychiatric conditions can be mimicked by structural brain pathologies, and these should only be diagnosed after a thorough medical assessment.

Assessment of coma

Management of coma is a time-sensitive process. The clinical approach to an unconscious patient should be structured. Figure 1 outlines a management algorithm. By necessity, it requires the clinician to deviate from the traditional sequential approach of history, examination, investigation and management;[1,2] instead, all four components can and should proceed in parallel through a team approach. Below, we consider the important aspects of each of the four domains in the traditional order.

Key components of the history

Comatose patients by definition cannot give a history. Gaining a collateral history from relatives or other witnesses to the event that preceded admission, or from the paramedics who attended the patient, can provide vital clues to the aetiology of the condition.[3] This can and should be done simultaneously with managing the patient.

Important aspects of the history include recent symptoms or illnesses, significant previous medical history, recent surgery or treatments and medication history. An understanding of the patient's existing functional status and premorbid condition is important; this helps to inform decisions regarding escalation of care and whether admission to intensive care and cardiopulmonary resuscitation are appropriate. An urgent review of the patient's previous medical notes and results can also provide essential clues.

Tim Cooksley *MB ChB(Hons) FRCP MRCP(Acute) is a Consultant in Acute Medicine at University Hospital of South Manchester and Honorary Consultant at The Christie, Manchester, UK. He is a past President of the Society for Acute Medicine. Competing interests: none declared.*

Mark Holland *MB BS FRCP MEd qualified from St George's Hospital Medical School, London, UK in 1988. He trained in geriatric and general internal medicine in London. In 2004 he moved to acute medicine. He is a past President of the Society for Acute Medicine. Competing interests: none declared.*

Differential diagnoses in an unconscious patient

Neurological	Metabolic	Diffuse physiological brain dysfunction	Psychiatric
Ischaemic stroke	Hypoglycaemia	Seizures	Psychiatric coma
Intracerebral haemorrhage	Hyperglycaemia	Alcohol intoxication	Malingering
Subarachnoid haemorrhage	Hyponatraemia	Opioid toxicity	
Subdural haematoma	Hypernatraemia	Drug overdose	
Brain tumour	Hypercalcaemia	Poisoning	
Cerebral lymphoma	Addisonian crisis	Hypothermia	
Multiple brain metastases	Hypothyroidism	Neuroleptic malignant syndrome	
Central nervous system infection	Uraemia	Serotonin syndrome	
Cerebral abscess	Hypercapnia		
Cerebral oedema	Septic encephalopathy		
Hydrocephalus			
PRES			
Trauma			
Venous sagittal sinus thrombosis			

PRES, posterior reversible encephalopathy syndrome.

Table 1

Paramedic teams or bystander witnesses may notice additional clues, such as used syringes or evidence of other recreational drug use, alcohol, empty medication packets or a suicide note. The paramedics are likely to have instituted pre-hospital treatments; it is important to ascertain the patient's response to these and to enquire about their conscious state at the scene to assess whether they are more or less responsive when reviewed.

Clinical examination of the unconscious patient

Determining unresponsiveness: initially, the patient has their eyes closed with a lack of facial expression, and is oblivious to environmental stimuli. A stepwise approach evaluates response to graded stimuli:[3]

- **verbal stimulus** – 'Can you hear me?' or 'Are you OK?'
- **tactile stimulus** – to either the hands or face
- **noxious stimulus** – which should be intense but not cause injury. Pressure on the supraorbital ridge or nail bed pressure is appropriate.

Neurological assessment: initial neurological examination focuses on determining the level of consciousness using the Glasgow Coma Scale (GCS) score (Table 2).

Assessment of the cranial nerves and motor response to pain should be performed. Pupil examination can provide useful clues as to the aetiology:[1]

- **small pupils (<2 mm)** – can be caused by either opioid toxicity or a pontine lesion
- **midsize pupils (4–6 mm) unresponsive to light** – can be the result of a midbrain lesion
- **maximally dilated pupils (>8 mm)** – can be caused by drug toxicity (amphetamines, cocaine) or oculomotor nerve pathology
- **unilateral fixed pupil** – from a IIIrd cranial nerve lesion.

Motor function is assessed by noxious stimuli as described above. It is important to distinguish between purposeful and reflexive responses.[3] Purposeful responses include the patient following commands, pushing the examiner away, localizing to the noxious stimulus and reaching for airway adjuncts. Reflexive responses are withdrawal, flexion or extension in response to the stimulus.

Fundoscopy can reveal key diagnostic findings, for example papilloedema in patients with hypertensive crisis and posterior reversible encephalopathy syndrome (PRES; see below), or subhyaloid haemorrhage in patients with subarachnoid haemorrhage.

General physical examination: doctors with a sensitive sense of smell may recognize the musty smell of hepatic encephalopathy or the garlic smell associated with organophosphate poisoning. While alcohol can be smelt on the breath of an unconscious patient, it is strongly recommended that all unconscious patients who appear to be intoxicated are fully assessed for other causes of unconsciousness, as the alcohol can be masking the true cause of unconsciousness, for example a head injury. Look for potential drug injection sites (groins, arms) or sites of subcutaneous insulin injections.

Breathing pattern abnormalities can provide useful clues:

- **Cheyne–Stokes breathing** can occur with many underlying pathologies and is not helpful in differentiating between diagnoses in the unconscious patient.
- **Ataxic breathing** (Biot respiration) is an abnormal pattern of breathing characterized by groups of quick, shallow inspirations followed by regular or irregular periods of apnoea; it indicates a lesion in the lower pons.
- **Central neurogenic hyperventilation** is an abnormal pattern of breathing characterized by deep and rapid breaths at a rate of at least 25 breaths per minute, and indicates a lesion in the pons or midbrain.

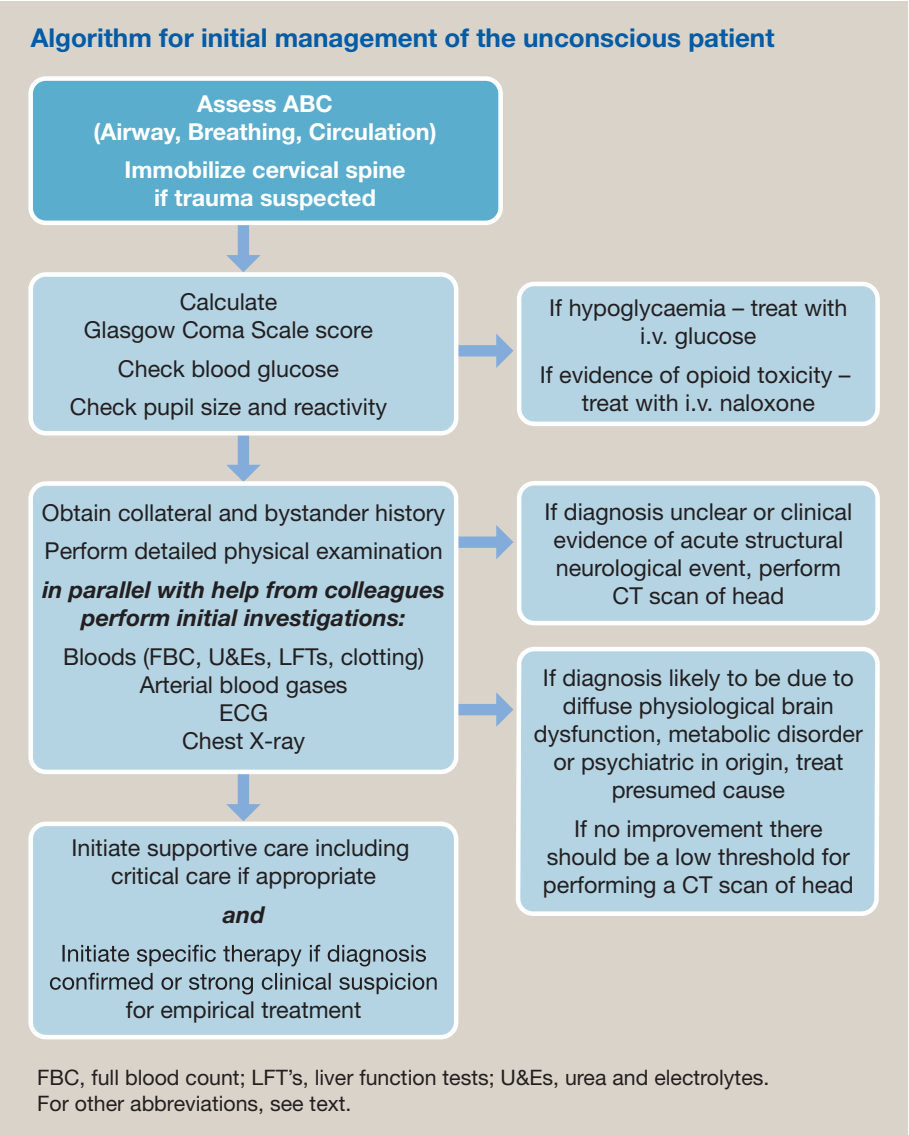

Figure 1

The GCS

Eye opening	Movement	Verbal
4 — Spontaneous	6 — Obeys commands	5 — Oriented
3 — To speech	5 — Localizes to pain	4 — Confused
2 — To pain	4 — Withdraws from pain	3 — Inappropriate words
1 — None	3 — Abnormal flexion to pain	2 — Incomprehensible sounds
	2 — Extensor response to pain	1 — None
	1 — No response	

Table 2

Investigations

- Blood glucose
- Urea and electrolytes
- Calcium
- Liver function tests
- Clotting screen
- Toxicology screen, including paracetamol and salicylate concentrations
- Electrocardiogram (ECG)
- Chest X-ray
- Arterial blood gases, including carbon monoxide concentrations.

In addition, blood cultures should be taken from patients with fever or features of sepsis. Urgent imaging of the brain is extremely important, especially if the cause of the coma is unclear; if the cause of coma is not obvious from the initial rapid assessment, a structural pathology should be considered.[1,3]

Computed tomography (CT) of the head and brain is the initial imaging modality of choice to exclude common pathologies such as subarachnoid haemorrhage, subdural haematoma, stroke or mass lesions. Common abnormalities seen on CT imaging are listed in Table 3. If CT imaging of the brain is normal and the diagnosis remains unclear, further imaging with

magnetic resonance scanning can be needed depending on clinical circumstances.

Lumbar puncture: in the absence of a contraindication, there should be a low threshold for performing a lumbar puncture, especially when the diagnosis of the coma is unclear and/or a central nervous system infection is suspected. The key components of a lumbar puncture are:

- measurement of the opening pressure
- description of the cerebrospinal fluid (CSF) appearance (colour, turbidity, bloodstaining)
- CSF analysis:
  - cell count (white cell count and red cell count)
  - Gram stain
  - glucose (with a contemporaneous plasma glucose)
  - protein
  - culture
  - consider sending samples for polymerase chain reaction testing and viral titres, India ink staining and cryptococcal antigen depending on the clinical situation.

Electroencephalography (EEG): EEG should be performed in patients suspected of having non-convulsive status epilepticus. This is prolonged seizure activity in the absence of motor signs and is more common in elderly patients. Clinically, it can be suggested by patients appearing to stare into space, nystagmus-like eye movements, lip smacking or myoclonic jerks.[4]

Management of coma

Every comatose patient is in a potentially life-threatening situation. Initial management should be performed in parallel with the assessments already discussed.

The ABC (Airway, Breathing, Circulation) approach should be used. If there is a history or suspicion of trauma, the cervical spine should be immobilized. Intubation should be considered in patients who cannot protect their own airway or are unconscious and have an ineffective respiratory drive and poor oxygenation. A GCS score of $\leq$8 should prompt consideration of the need for airway protection. If raised intracranial pressure is suspected, the patient should be managed in a 30° position.

While the ABC assessment is taking place, colleagues should be establishing intravenous (i.v.) access, connecting cardiac and oxygen saturation monitoring and starting oxygen therapy if indicated. Hypotension should initially be treated with i.v. fluid resuscitation, but with consideration of inotropic support if the blood pressure does not respond. Involvement of critical care colleagues should be sought at an early stage if the cause of unconsciousness is not immediately reversible.[5]

Specific therapies

Treatment depends on the underlying aetiology. 'Coma cocktails' should be avoided.[3] In cases where there is clinical suspicion of toxicity, specific antidotes should be used:

Hypoglycaemia – this must always be excluded. If present, it should be monitored and treated with an i.v. infusion (over 10–15 minutes) of glucose 20% 75–80 ml, or glucose 10% 150–160 ml. Glucagon (1 mg intramuscular (i.m.)) can be used but can take up to 15 minutes to act and is ineffective in patients with liver disease, depleted glycogen stores or malnutrition. Co-administration of i.v. thiamine should be considered in all patients felt to be at risk of Wernicke encephalopathy, for example those abusing alcohol.

If a patient presents with hypoglycaemia, it is essential to determine whether they have diabetes mellitus. If they have, their normal medication should be determined. If they do not, liver disease, overdose, Addison disease and malnutrition should be considered.

Opioid toxicity – naloxone (0.4–2 mg i.v.) should be administered. Naloxone is a competitive opioid antagonist, and the dose required depends upon the amount of opioid taken. Relapse is common as naloxone has a short half-life (20–30 minutes) and recurrent injections or an infusion can be required. Naloxone can be administered intravenously, intramuscularly or intranasally.

Benzodiazepines – administration of i.v. flumazenil can be considered in confirmed benzodiazepine toxicity. However, it is contraindicated in patients with a history of seizures, and it can provoke seizures with concomitant tricyclic overdose.

Severe hyponatraemia – this is a complex condition and, in unconscious patients, should be managed by experts in a critical care setting. It is important to assess whether the hyponatraemia

Basic CT findings of key neurological conditions that can be seen in unconscious patients

Disease process	CT scan findings
Subarachnoid haemorrhage	Haemorrhage into CSF spaces (cisterns, convexity). Complicated by hydrocephalus in about 20% of cases. Is 98% sensitive at 12 hours after the onset of symptoms
Subdural haematoma	Sickle- or crescent-shaped collection of blood (usually over the convexity). Can be either acute or chronic
Ischaemic stroke	The earliest change seen is a loss of grey–white matter differentiation at the site of ischaemia
Tumour	Hypodense lesion. Usually surrounded by oedema (from loss of the integrity of the blood–brain barrier, allowing fluid to pass into the extracellular spaces)
Hydrocephalus	Dilatation of the ventricles
PRES	Classically vasogenic oedema of the bilateral parietal–occipital lobes. Usually symmetrical. A significant proportion have atypical findings

Table 3

is acute or chronic and, unless the patient is having seizures, to correct it gradually to avoid central pontine myelinolysis.

Hypercalcaemia – the first-line therapy is i.v. sodium chloride 0.9%; thereafter, calcitonin, i.v. bisphosphonates and i.v. glucocorticoids can be considered depending on the serum calcium concentration, the underlying cause and the response to sodium chloride 0.9%.

Toxicity with methanol, lithium, salicylate or ethylene glycol – renal replacement therapy, such as haemofiltration, may be required.

Treatment of the comatose patient with a neurological cause

In comatose patients with an acute neurological condition, urgent discussion with neurosurgeons or and neurologists is necessary to determine further management.

If bacterial meningitis is suspected, empirical antibiotic treatment should be commenced pending a lumbar puncture; if encephalitis is suspected, i.v. aciclovir should be given as soon as possible.

PRES is a combined clinical and radiological syndrome characterized by headaches, encephalopathy, seizures and visual loss. It is associated with accelerated hypertension, pregnancy, sepsis and chemotherapeutic agents. Management is aimed at controlling blood pressure, and controlling seizures with i.v. anticonvulsants and withdrawal of trigger agents.

Prognosis of coma

The outcome and prognosis of coma is determined by the underlying cause. Reversible causes of coma are generally more likely when CT of the brain is unremarkable and the patient has no focal neurology. Patients not responding to initial treatment who remain unconscious are likely to require critical care admission unless withdrawal of treatment and palliation of symptoms is appropriate, for example in a patient with a catastrophic brain injury. Accurate prognosis is often not possible in the early assessment of coma. ◆

KEY REFERENCES

1 Cooksley T, Rose S, Holland M. A systematic approach to the unconscious patient. *Clin Med (Lond)* 2018; **18:** 88–92.
2 Wijdicks E. Coma. *Practical Neurol* 2010; **10:** 51–60.
3 Edlow J, Robinstein A, Traub S, et al. Diagnosis of reversible causes of coma. *Lancet* 2014; **384:** 2064–76.
4 Zubler F, Koenig C, Steimer A, et al. Prognostic and diagnostic value of EEG signal coupling measures in coma. *Clin Neurophysiol* 2016; **127:** 2942–52.
5 Horsting M, Franken M, Meulenbelt J, et al. The etiology and outcome of non-traumatic coma in critical care: a systematic review. *BMC Anesthesiol* 2015; **15:** 65.

FURTHER READING

Christofi G. A clinical approach to coma: neurological assessment of the comatose patient. *Anaesth Intensive Care Med* 2022; **23:** 764–75.

Dubosh N, Edlow J, Lefton M, et al. Types of diagnostic errors in neurological emergencies in the emergency department. *Diagnosis* 2015; **2:** 21–8.

O'Callaghan P. Transient loss of consciousness. *Medicine* 2012; **40:** 427–30.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 32-year-old woman was seen in the emergency department. She was 28 weeks' pregnant. The history was taken from her husband. The woman had been well until 2 days before admission. He described her behaviour being 'odd', and she had developed a fixation with sensing an abnormal smell. There was no headache. While watching television, she had had a clonic seizure. She had previously been well and had no significant previous medical history. This was her first pregnancy. She was taking folic acid supplements.

On clinical examination, the Glasgow Coma Scale score was 5/15 (eyes 1, motor 2, verbal 2). Her temperature was 38.5°C, pulse 80 beats/minute and blood pressure 130/80 mmHg. There were no localizing neurological signs. Urine dipstick testing was normal.

Investigations

- Full blood count, urea and electrolytes and liver function tests were all normal
- Chest X-ray was normal
- A CT scan performed 4 hours after her seizure was normal
- Cerebrospinal fluid:
  - <1 white cell/microlitre
  - Protein 2.1 g/litre (0.15–0.45)
  - Xanthochromia negative

What is the most likely diagnosis?

A. Acute stroke
B. Acute subdural haematoma
C. Bacterial meningitis
D. Viral encephalitis
E. Sagittal sinus thrombosis

Question 2

A 65-year man presented with a 2-day history of intermittent fevers, visual loss and acute generalized headache. There was no complaint of speech disturbance or limb weakness. He was being treated with chemotherapy for T cell prolymphocytic leukaemia but had no other significant medical history.

On clinical examination, his temperature was 37.9°C and blood pressure 238/137 mmHg. He deteriorated rapidly and developed grand mal seizures, after which his Glasgow Coma Scale score was measured as 7/15.

What is the most likely diagnosis?

A. Central nervous system involvement with leukaemia
B. Bacterial meningitis
C. Viral meningitis
D. Posterior reversible encephalopathy syndrome (PRES)
E. Stroke

Question 3

A 48-year-old man presented to the emergency department with a Glasgow Coma Scale (GCS) score of 6/15 after being found unconscious at home by his sister when he failed to answer his mobile phone. He smelt strongly of alcohol although his sister said he did not usually drink alcohol and he does not smoke. He had been taking diazepam 2 mg as required for many years for anxiety and insomnia. On clinical examination, there was no sign of trauma. His temperature was 37.0°C, heart rate 104 beats/minute and regular, blood pressure 108/72 mmHg, and oxygen saturations 100% on 15 litres of oxygen delivered via a non-rebreather mask.

What is the most appropriate management?

A. Await recovery from excessive alcohol ingestion
B. Administer flumazenil
C. The ABCDE approach can be skipped as we have enough information
D. Perform a CT brain scan
E. Discontinue oxygen as the patient may be retaining carbon dioxide.