Diagnosis of reversible causes of coma

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Because coma has many causes, physicians must develop a structured, algorithmic approach to diagnose and treat reversible causes rapidly. The three main mechanisms of coma are structural brain lesions, diffuse neuronal dysfunction, and, rarely, psychiatric causes. The first priority is to stabilise the patient by treatment of life-threatening conditions, then to use the history, physical examination, and laboratory findings to identify structural causes and diagnose treatable disorders. Some patients have a clear diagnosis. In those who do not, the first decision is whether brain imaging is needed. Imaging should be done in post-traumatic coma or when structural brain lesions are probable or possible causes. Patients who do not undergo imaging should be reassessed regularly. If CT is non-diagnostic, a checklist should be used use to indicate whether advanced imaging is needed or evidence is present of a treatable poisoning or infection, seizures including non-convulsive status epilepticus, endocrinopathy, or thiamine deficiency.

Introduction

Many patients present to emergency departments with an altered state of consciousness. The state of coma is marked by a lack of awareness and response to external stimuli; patients cannot be roused. There are many causes. A history of head injury, cardiac arrest, or hypoglycaemia, or CT of the brain will disclose a clear diagnosis in many cases.

Physicians should look out for reversible causes of coma (table 1), in which a specific action taken by the treating physician might reverse it. In general, reversible causes of coma are likely when neurological examination does not show focal deficits and CT is unrevealing,[1,2] although in some patients, CT will show a reversible cause such as a compressive mass or acute hydrocephalus.

General practitioners, specialists in internal medicine or intensive care, hospital doctors, and emergency physicians must have basic skills in the initial assessment and management of comatose patients. Rapid stabilisation of vital functions should be followed by a focused investigation to find and treat reversible causes. If a systematic diagnostic approach is not used, physicians could undertake many tests, which could prove unnecessary or falsely reassuring. We introduce here a stepwise approach based on the underlying principles of coma pathophysiology combined with knowledge of the reversible causes that should increase the likelihood of establishing an early correct diagnosis.

Search strategy and selection criteria

We searched PubMed from Jan 1, 1970, to March 1, 2013, for articles with the search term "coma" in the title or abstract. Additionally, to capture other possible sources of relevant literature, we did separate searches for "coma" (title or abstract) plus "basilar artery thrombosis", "stroke", "non-convulsive status epilepticus", "meningitis", "CNS infection", "endocrinopathy" and "Wernicke's encephalopathy" (each of these in the title or abstract). We also searched the bibliographies of selected articles and articles from the authors' personal libraries including classic textbooks on the subject of coma. We restricted our search to articles published only in English.

Basic pathophysiological considerations

Knowledge of the underlying mechanisms of coma facilitates correct diagnosis. Arousal and awareness are inter-related functions although a change in one is not always associated with a similar change in the other.[3,4] The anatomical seat of arousal is the ascending reticular activating system in the brainstem. Neurons of this system originate in the dorsal pons and midbrain, connect in the thalamus, and project to several areas in the cortex. The cortex processes, integrates, and gives context to the information provided to it thus generating awareness. Injury to any of these areas or their connections can result in impaired consciousness.

Causes of coma are thus classed in three groups—structural brain disease, diffuse neuronal dysfunction (resulting from various conditions that produce a general state of depressed neuronal function), and psychogenic unresponsiveness.[4] Other than psychiatric causes, all these diagnoses affect the cerebral cortex, the ascending reticular activating system, or their connections. Bilateral cortical diseases causing coma can be structural (eg, bilateral subdural haematoma) or result from diffuse neuronal dysfunction (eg, severe hyperglycaemia). Destructive lesions involving the ascending reticular activating system in the brainstem or thalamus also produce coma, as does a cerebellar mass or oedema that compresses the dorsal brainstem. We should point out that isolated unilateral hemispheric lesions (without displacement of other structures or pre-existing severe contralateral hemispheric disease) do not cause coma.

Because the skull is unyielding, compensation for increasing intracranial mass is initially accomplished by translocation of cerebrospinal fluid (CSF) or blood, but as the mass increases in size compensatory mechanisms begin to fail. Structures from one intracranial compartment shift into another. Displacement of brain tissue (herniation) does not follow a single line of force. The finding that lateral tissue displacement is more closely related to level of consciousness than is downward shift challenges the classic concept of transtentorial herniation (compression of the midbrain by the displacement of the temporal uncus caused by an expanding hemispheric mass).[5–7]

The rate of progression of mass size is important. A slowly growing posterior fossa tumour can cause substantial brainstem distortion without producing changes in mental status, whereas an acute haemorrhage of similar size can cause coma (figure 1). Shifts in brain tissue can also cause ischaemic infarctions (from compression of cerebral arteries against the rigid dura of the falx or tentorium) or obstructive hydrocephalus; both can lead to abrupt deterioration in mental status.

Some causes of coma (eg, hypoglycaemia, acute hydrocephalus) generally respond rapidly to treatment (glucose administration, placement of an external ventricular drain). Others, such as coma caused by bacterial meningitis or a subdural haematoma, can take longer to resolve after initiation of treatment (intravenous antibiotics or surgical decompression). A reversible cause can become irreversible if not promptly recognised and treated. For example, a patient comatose from subdural haematoma that is drained rapidly will probably respond favourably, whereas one with delayed diagnosis and treatment could fare less well. Similarly, severe and prolonged hypoglycaemia can lead to brain lesions that become permanent.[8,9] Diffuse neuronal dysfunction resulting from acute hyperglycaemia or anoxic-ischaemic injury can also lead to structural damage.

Coma resulting purely from psychiatric illness is rare. Patients with a history of psychiatric illness can present

	Usual treatment	Comments
Structural brain disease*		
Brain mass	Surgical removal, possible steroids (tumour, abscess)	Steps are a function of many variables including cause of mass
Anoxic-hypoxic brain disease with return of spontaneous circulation after cardiac arrest	Therapeutic mild hypothermia (or at least strict maintenance of normothermia)	..
Raised intracranial pressure	Elevate head of bed, intravenous mannitol, hypertonic saline, hyperventilation and corticosteroids, loosen any constricting bandages or collars	When to treat, and which agent to use is decided case-by-case
Subdural or epidural haematoma	Consider surgical drainage	..
Intracerebral haemorrhage	Hemostatic therapy to correct coagulopathy, consider blood pressure control and possible surgical drainage	Investigate underlying vascular lesion
Acute ischaemic stroke	Thrombolytic therapy	Investigate underlying vascular lesion
Hydrocephalus	Ventriculostomy and drainage	..
Cerebral oedema resulting from stroke	Decompressive craniectomy	..
Cerebellar oedema resulting from stroke	Suboccipital decompressive craniectomy	..
Cerebral venous sinus thrombosis	Intravenous heparin	Consider endovascular intervention for large clots
Sepsis	Intravenous antimicrobials; surgical drainage of any abscess; goal-directed Intravenous fluids	Choice of empirical drugs depends on epidemiological context, local antibiotic resistance patterns, other patient-related factors such as allergies and hepatic and renal function
CNS infections	Antimicrobials, drainage for brain abscess, consider steroids for meningitis	Choice of empirical drugs depends on epidemiological context, local antibiotic resistance patterns, other patient-related factors such as allergies and hepatic and renal function
Non-convulsive or minimally convulsive status epilepticus	Anti-epileptic drugs	Consider EEG when persistent coma after convulsions and in sedated or paralysed patients
Diffuse neuronal dysfunction		
Hypoglycaemia	50% dextrose	Look for and treat precipitant
Hyperglycaemia, diabetic or alcoholic ketoacidosis	Intravenous saline, insulin	Look for and treat precipitant
Hyponatraemia	Hypertonic saline	Look for and treat precipitant
Hypercalcaemia	Intravenous saline, furosemide, other drugs	Look for and treat precipitant
Hyperammonaemia	Treat underlying condition	Look for and treat precipitant
Renal failure	Dialysis	Investigate cause
Hepatic encephalopathy	Lactulose	Look for and treat precipitant
Thyroid storm	Anti-thyroid medications and β-blockers	Look for and treat precipitant
Myxoedema coma	Hormone replacement	Look for and treat precipitant
Adrenal crisis	Hormone replacement and intravenous fluids	Look for and treat precipitant
Pituitary apoplexy	Possible surgery, hormone replacement	Look for and treat precipitant
Wernicke's encephalopathy	Intravenous thiamine	..

(Table 1 continues on next page)

	Usual treatment	Comments
(Continued from previous page)		
Toxins		
Sedative hypnotic agents	Supportive care	Ethanol, barbiturates, benzodiazepines
Opioids	Naloxone	Heroin, oxycodone, hydrocodone
Dissociative agents	Supportive care	Ketamine, phencyclidine
MDMA	Treat hyponatraemia if present	..
Inhalants	Treat methaemoglobinaemia if present (alkyl nitrites)	Alkyl nitrites, nitrous oxide, hydrocarbons
Toxic alcohols	Fomepizole, bicarbonate	Methanol, ethylene glycol
Histotoxic agents causing hypoxia	Hydroxocobalamin for cyanide	Cyanide, hydrogen sulphide
Carbon monoxide	Hyperbaric oxygen	..
Methaemoglobinaemia	Oxygen and methylene blue	Alkyl nitrites, nitrous oxide, hydrocarbons
Psychiatric medications	Bicarbonate (wide QRS interval on ECG)	Antipsychotics, antidepressants
Antiepileptic drugs	Supportive care	Phenytoin, valproate, carbamazepine
Clonidine	Naloxone	..
Membrane-stabilising β blockers	Glucagon, intravenous lipid emulsion	Propranolol
Cholinergic agents	Atropine, pralidoxime	Organophosphates, carbamates
Fumigants	Supportive care	Methyl bromide
Hypoglycaemic agents	Dextrose, octreotide (sulfonylureas)	Sulfonylureas, insulin, ingestion of unripe ackee fruit, meglitinides
Herbicides	Supportive care	Glufosinate
Isoniazid	Pyridoxine	..
Rodenticides	Supportive care	Compounds 1080 and 1081; tetramine
Salicylates	Bicarbonate	Aspirin, oil of wintergreen
Simple asphyxiants	Oxygen	Nitrogen, helium, argon
Neuroleptic malignant syndrome	Benzodiazepines	Consider pharmacological paralysis
Serotonin syndrome	Benzodiazepines, cyproheptadine	Consider pharmacological paralysis

EEG=electroencephalography. MDMA=methylenedioxymethamphetamine. ECG=electrocardiogram. *Consult neurologist, neurosurgeon, or both.

Table 1: **Reversible causes of coma by diagnosis**

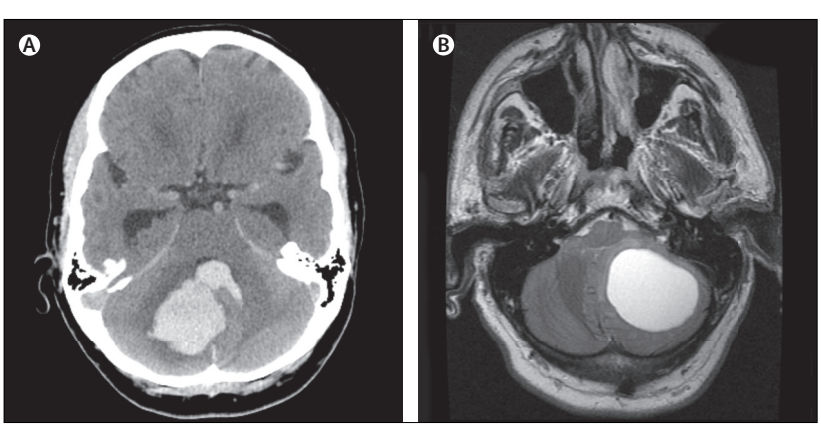

Figure 1: **Two patients with similar sized cerebellar lesions of differing cause and different mode of onset**
(A) This 51-year-old patient presented in coma with a full outline of unresponsiveness (FOUR) score of E0 M1 B2 (pupils 3 mm and fixed, corneal reflexes intact) R1. CT shows a cerebellar haematoma with blood in the fourth ventricle and hydrocephalus. He underwent surgical decompression; 2 years postoperatively he was ambulant with a walker but independent. (B) This 48-year-old patient presented with several weeks of vague dizziness and mild left-sided neck pain. He was awake and alert; neurological examination was normal except for the presence of vertical and direction-changing horizontal nystagmus. Axial T2-weighted MRI shows a large tumour with significant compression and distortion of the brainstem. A benign tumour was removed and he was neurologically intact.

with altered mental status caused by drug overdose or drug side-effects, such as neuroleptic malignant syndrome (antipsychotic or dopamine-blocking drugs) and serotonin syndrome (serotonin reuptake inhibitors).[10] Structural brain disorders can also mimic psychiatric illness. Patients with bilateral thalamic strokes, generally involving the artery of Percheron (a variant that supplies the medial thalamus bilaterally; figure 2) have been misdiagnosed with conversion disorders.[11,12] For all of these reasons, psychogenic coma should be diagnosed only after a thorough medical and neurological assessment.

Principles in the assessment of comatose patients

Initial stabilisation

As with any unstable patient, the treating team should spend the first minutes confirming a patent airway, intubating when necessary to ensure adequate oxygenation, ventilation, and protection from aspiration, establishing intravenous access, administering saline if the patient is hypotensive, and treating hypoglycaemia if present. Until trauma of the cervical spine has been

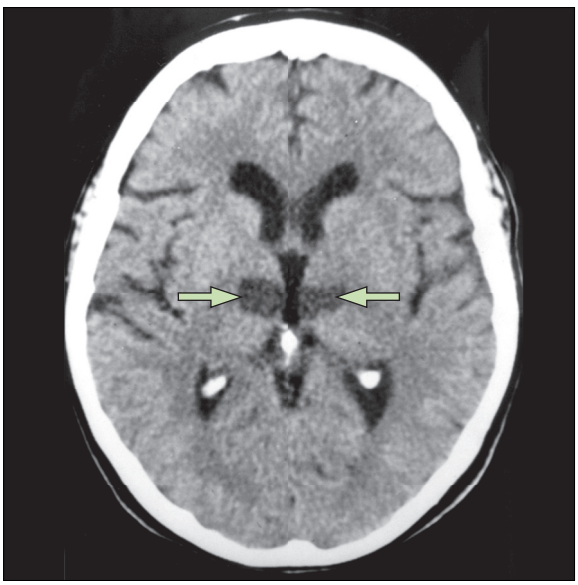

Figure 2: **A hypertensive patient who presented with abrupt onset of coma**
Delayed CT shows bilateral hypodensities (green arrows) in both paramedian thalami resulting from a stroke involving the artery of Percheron, a variant branch of the posterior cerebral artery that supplies both sides of the medial thalamus (courtesy of Louis R Caplan).

excluded (by history or imaging), it should be immobilised. Oxygen saturation should be maintained at more than 96% with supplemental oxygen. If intracranial pressure might be raised, the head of the bed should be kept at 30°; the head of the bed should be flat if posterior circulation stroke is a possible cause. These crucial therapeutic steps take precedence over obtaining history.

We do not recommend routine administration of a coma cocktail (combinations of intravenous thiamine, glucose, naloxone, flumazenil, or physostigmine).[13] Standard practice includes testing for and treating hypoglycaemia. We recommend use of naloxone when the clinical presentation supports opioid intoxication, but caution that its indiscriminate use can precipitate withdrawal symptoms in opioid-habituated patients with coma of another cause. Flumazenil can precipitate benzodiazepine withdrawal, with life-threatening consequences. Routine use of physostigmine or other non-specific analeptic arousal agents in the treatment of toxin-induced coma is unnecessary; supportive care alone is superior.

After initial stabilisation, the priority shifts to answering the following questions. Is the patient comatose? If so, to what degree is the level of consciousness altered? Is there a potentially reversible cause?

Initial clinical assessment

The components of the initial assessment are the history, physical examination, and laboratory tests (figure 3). The history and physical examination aim to distinguish a structural cause from diffuse neuronal dysfunction or psychiatric cause.

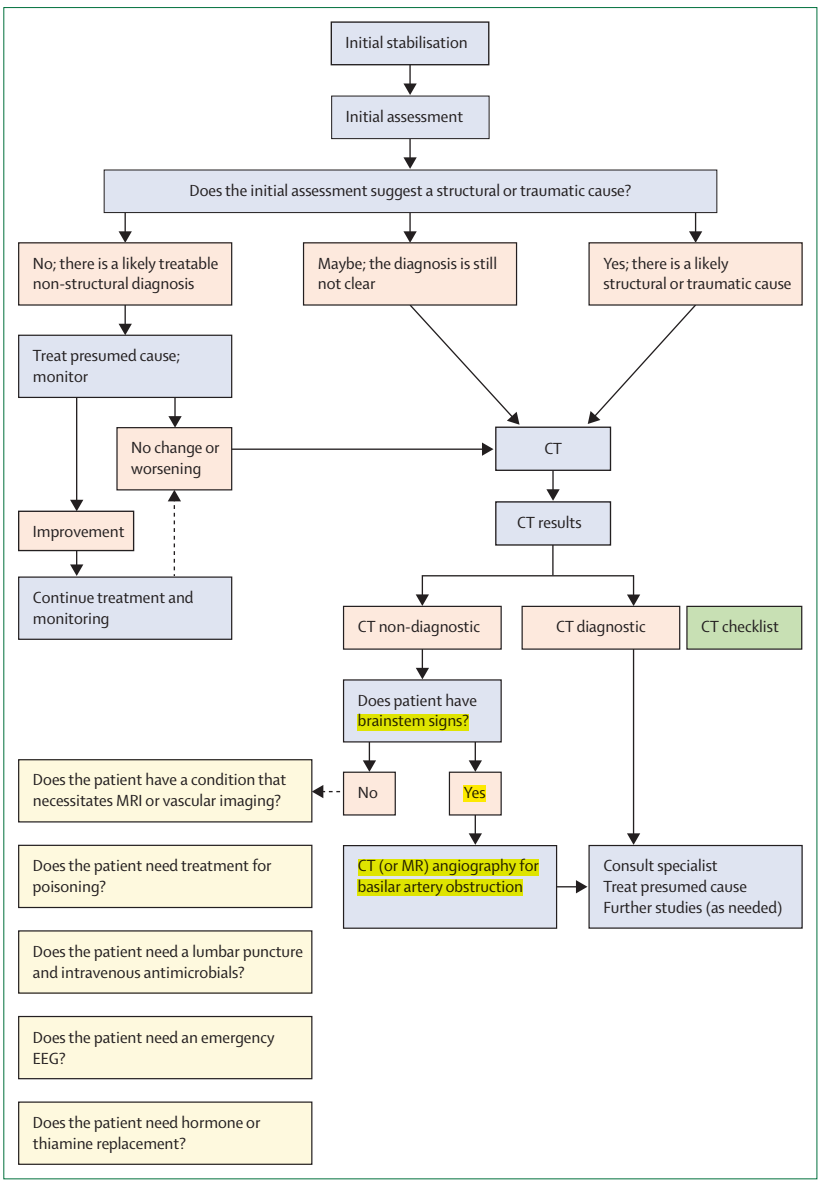

Figure 3: **Algorithm for diagnosis of cause of coma**

History

Physicians should try to obtain available information from bystanders, friends or family, prehospital personnel, or police officers. Such information is indirect and should be interpreted cautiously (eg, a patient with alcohol intoxication could also have a subdural haematoma). Other potential sources of information include previous medical records (if the patient has been positively identified), medical alert bracelets or cards, medication lists, or a pharmacy telephone number in the patient's belongings. Because fragments of information tend to become available incrementally, the working diagnoses should evolve as new information emerges. At the same time as this initial assessment, physicians should measure

blood glucose, send blood samples for analysis, and obtain an electrocardiogram (ECG), which can provide rapid and inexpensive clues of a possible toxic cause.

The physician also needs to establish onset, evolution, associated symptoms, and previous history. Sudden onset of coma suggests a stroke, seizure, or poisoning. A preceding thunderclap headache suggests aneurysmal subarachnoid haemorrhage, parenchymal intracranial haemorrhage, cerebral venous sinus thrombosis, idiopathic intracranial hypotension, pituitary apoplexy, or cerebellar stroke.[14] Gradual onset suggests an expanding mass or inflammatory process. A history of seizures or a seizure at onset, known psychiatric disease, vascular risk factors, and anticoagulant use all suggest other possible diagnoses. Knowledge that the coma was caused by a cardiac arrest has immediate therapeutic implications given the benefits of therapeutic hypothermia.[15,16] The presence or absence of trauma must also be established. Historical information, however, is generally sparse and uncertain, which makes the physical examination more important.

	Suggested causes
History	
Sudden onset	Stroke, seizure, drug overdose
Gradual onset	Tumour or inflammatory CNS disease
Preceding thunderclap headache	Subarachnoid haemorrhage, intracranial haemorrhage, cerebral venous sinus thrombosis, pituitary apoplexy, cerebellar stroke
Seizure at onset	Convulsive or non-convulsive status epilepticus, poisoning by carbon monoxide, cyanide, hypoglycaemic agents, organophosphates, bupropion, γ hydroxybutyrate, baclofen, tricyclic antidepressant, carbamazepine, propoxyphene
History of cancer	Brain metastases
Bleeding diathesis	Intracerebral haemorrhage, subdural haematoma
Hypercoagulable state	Cerebral venous sinus thrombosis
Physical examination	
Cachexia	Metastatic cancer to brain
Hyperpyrexia	Sepsis, focal infections (including CNS infections), phencyclidine or ketamine intoxication, neuroleptic malignant syndrome, serotonin syndrome, massive pontine haemorrhage, subarachnoid haemorrhage, heat stroke, hypothalamic injury, salicylates, cholinergic agents, MDMA
Hypothermia	Hypoglycaemia, alcohol and sedative/hypnotic or opioid intoxication, sepsis, myxoedema, adrenal crisis, pituitary apoplexy
Tachycardia	Antidepressants, antipsychotic or ketamine intoxication, adrenergic hyperactivity from acute structural brain injury
Bradycardia	β blockers with membrane-stabilising activity, clonidine, organophosphates, sedative-hypnotic agents, γ-hydroxybutyrate, opioids, intracerebral pressure (including hydrocephalus)
Hypertension	Hypertensive encephalopathy, posterior reversible encephalopathy syndrome, eclampsia, intoxication with phencyclidine, ketamine, MDMA, clonidine (early), non-specific response to acute CNS disease; the combination of hypertension and bradycardia can indicate raised intracranial pressure
Hypotension	Sepsis, tricyclic antidepressants, sedative-hypnotic agents, cyanide, phenothiazines, and clonidine
Fast respiratory rate	Early sepsis and metabolic acidosis of any cause, diencephalic damage, salicylate intoxication
Slow respiratory rate	Sedative-hypnotic or opioid overdose, organophosphate compounds, terminal event with medullary involvement
Odours on breath	
Dirty lavatory	Uraemia
Fruity	Ketoacidosis
Musty or fishy	Hepatic encephalopathy
Garlic	Organophosphates
General examination	
Tongue laceration	Seizure
Goitre	Myxoedema coma
Meningismus	Meningitis or subarachnoid haemorrhage
Ascites, jaundice, caput medusa	Hepatic failure
Peripheral oedema	Renal and hepatic failure, myxoedema
Increased secretions	Organophosphate, ketamine intoxication
Decreased bowel sounds	Opioids
Increased bowel sounds	Organophosphates

(Table 2 continues on next page)

Physical examination

The general examination can give various diagnostic clues (table 2).[17] In particular, abnormal vital signs should be accounted for. Non-invasive measurement of end-tidal carbon dioxide can help to assess ventilation. Single values can be inaccurate, but raised or increasing values suggest hypercarbic respiratory failure. Various combinations of findings suggest a specific toxic syndrome.

The main objectives of the neurological examination are to identify lateralising or focal findings, recognise signs of brainstem dysfunction, and define its severity (table 3). First, the physician should rapidly decide whether the lesion is in one hemisphere causing mass effect, in both hemispheres, or in the brainstem. This investigation starts with assessments of the motor responses and brainstem reflexes. Most comatose patients have normal brainstem reflexes and many withdraw only to noxious stimuli. In such patients, the abnormality is in the supratentorial hemispheres and can be structural (which might show on CT) or physiological (which will not). Abnormal motor responses do not differentiate well between an acute structural injury to the hemispheres or brainstem; the presence of abnormal pupillary or brainstem reflexes has more localising value. Other findings can refine the differential diagnosis and focus the diagnostic assessment. Brainstem syndromes can be divided into intrinsic brainstem disease and brainstem displacement syndromes, although the two do overlap. Intrinsic brainstem lesions are characterised by extensor or flexor posturing, skew deviation (vertical misalignment of the eyes), miosis, or anisocoria and, in some cases, abnormal oculovestibular responses (table 3).

Four elements of the examination help to further define the depth of coma and its localisation: level of consciousness, brainstem assessment, motor examination, and assessment of breathing patterns. Various coma scores incorporate these elements to give a more objective and reproducible assessment of level of consciousness. The two most commonly used are the

Glasgow Coma Scale (GCS) and the Full Outline Of Unresponsiveness (FOUR) score; the latter better incorporates the four key elements (panel).[18]

The GCS was designed to assess patients with traumatic brain injury, but physicians use it in all forms of coma.[19] It loses discriminative value in intubated patients and those with very low scores, and it assesses brainstem function poorly. The FOUR score has been extensively validated in various medical environments (emergency departments, neurology, neurosurgery), and has excellent between-observer consistency;[20–22] it has better predictive value than the GCS in intubated patients and those with very low GCS scores.[23,24] For both scores, reporting the scores for each element rather than only the sum score improves usefulness.

The physician should test motor function by first observing any spontaneous movements or posturing, then responses to verbal commands, and finally response to noxious stimuli (by compression over the supraorbital nerve, temporomandibular joint, or nail bed). Observe for flexor or extensor reaction versus no movement at all.[4,17] Both sides should be tested since localisation to pain requires the patient's contralateral arm to cross the midline towards the noxious stimulus.[17] Some patients have myoclonus (focal twitches), which may also be present in patients with non-convulsive status epilepticus and renal, hepatic, and hypercarbic respiratory failure.

Imaging results cannot be properly interpreted without knowledge of whether brainstem signs are present. The main brainstem reflexes have localising value; they include pupillary response (size, reactivity, and symmetry), corneal reflex, oculocephalic reflex (so-called doll's eyes, provided that the cervical spine has been cleared), vestibulo-ocular reflex (cold caloric testing), and gag and cough reflexes. In one study of 115 comatose patients, presence of anisocoria and diminished pupillary light reflex were most closely associated with a structural cause.[25] In another study of 500 consecutive comatose patients without trauma, pupillary reflex and, to a lesser extent, oculocephalic reflex were associated with prognosis.[26] Infra-red pupillometry precisely measures pupil size and reactivity; however, its practical value is unknown.[27]

Eye movements have less localising value. Spontaneous roving eye movements indicate that the brainstem is intact, whereas skew deviation (vertical misalignment of the eyes) strongly suggests a brainstem lesion. Forced deviation of the eyes to one side generally indicates an ipsilateral hemispheric or contralateral pontine lesion. Seizures can cause eye deviation away from the side of the seizure focus.

Oculovestibular testing with ice water infusion is a simple, yet underused test. After trauma to the external ear canal or tympanum has been excluded, the patient's head should be placed at 30° up from horizontal, and iced water infused into the canal. In a comatose patient with an intact lower midbrain and pons, the eyes will tonically deviate towards the side of the irrigation.[2] Comatose patients will not have nystagmus (rapid component away from the side of irrigation); nystagmus implies intact cortical function consistent with psychogenic coma.[2]

The breathing pattern should be observed. Cheyne-Stokes respirations, seen with diffuse neuronal dysfunction, circulatory problems such as heart failure,

	Suggested causes
(Continued from previous page)	
Skin examination	
Bullae	Coma-bullae non-specific, classically associated with barbiturates
Cool skin with yellow tinge and puffy face	Myxoedema
Dark pigmentation	Adrenal crisis
Dry skin	Anticholingergic agents such as tricyclic antidepressants and antipsychotics
Purpura or petechiae	Thrombotic thrombocytopenic purpura, vasculitis, disseminated intravascular coagulopathy, sepsis with meningococcal, streptococcal, or staphylococcal species or rickettsia
Sweating	Organophosphate poisoning, hypoglycaemia, thyroid storm, sympathetic hyperactivity, neuroleptic malignant syndrome, serotonin syndrome
Needle track marks	Opioid overdose
Jaundice, caput medusa, palmar erythema, spider angiomata	Hepatic encephalopathy
Neurological findings	
Miosis	Opioid, organophosphate intoxication, clonidine
Mydriasis	Tricyclic antidepressant or MDMA intoxication
Horizontal nystagmus	Ethanol, anti-epileptic drugs, dissociative agents
Vertical nystagmus	Brainstem lesions, dissociative agents
Laboratory findings	
Hypoglycaemia	Insulin, sulfonylureas, ackee fruit ingestion, β blockers, meglitinides
Hyperglycaemia	Diabetic ketoacidosis, non-ketotic hyperosmolar coma
Hyponatraemia	MDMA, carbamazepine
Hypernatraemia	Inadequate free water intake in setting of hypovolaemia (and other states of disordered sodium homoeostasis)
Raised ammonia	Liver failure, valproic acid, urea cycle disorder
Blood gases	
Metabolic acidosis	Methanol, ethylene glycol, paraldehyde, isoniazid, or salicylate poisoning, lactic acidosis of any cause (including cyanide and hydrogen sulphide poisoning and Wernicke's encephalopathy), ketoacidosis, uraemia
Respiratory acidosis	CNS depressant (opioid, benzodiazepine, barbiturate), hypercarbic respiratory failure
Respiratory alkalosis	Central hyperventilation, salicylates
Methaemoglobinaemia	Alkyl nitrates
Anion gap metabolic acidosis	Cyanide, hydrogen sulphide, toxic alcohols, salicylates, all causes of lactic acidosis
Osmolar gap	Methanol and ethylene glycol
ECG findings	
Prolonged QTc interval	Tricyclic antidepressant or antipsychotic intoxication, various forms of acute structural brain injury
Prolonged QRS interval	Tricyclic antidepressants, phenothiazines, carbamazepine, propoxyphene, various forms of acute structural brain injury
Osborne waves	Hypothermia
Cerebral (inverted) T waves	Subarachnoid haemorrhage and other forms of acute structural brain injury

MDMA=methylenedioxymethamphetamine.

Table 2: **Clinical, laboratory, and ECG clues suggesting particular causes of coma**

	Neurological findings
Bilateral hemispheric	Spontaneous eye movements (roving, dipping*, ping-pong, nystagmoid jerks) Upward or downward eye deviation Intact oculovestibular reflexes Intact pupillary and corneal reflexes Variable motor responses Adventitious limb movements (subtle manifestations of seizures, myoclonus, asterixis)
Brainstem displacement from a hemispheric mass	Anisocoria or unilateral fixed and dilated pupil (predominant lateral displacement) Midposition fixed pupils (predominant downward displacement) Extensor or flexor posturing Central hyperventilation (diencephalic)
Brainstem displacement from a cerebellar mass	Direction-changing or vertical nystagmus from the cerebellar lesion Ocular bobbing† Absent corneal reflexes with intact pupillary reflexes Extensor or flexor posturing Facial or abducens nerve palsy Skew deviation (vertical misalignment of eyes) Internuclear ophthalmoplegia
Intrinsic brainstem lesion	Vertical nystagmus or bobbing Miosis (with pontine lesions) Internuclear ophthalmoplegia Variable pupillary and corneal reflexes (can both be absent) Absent oculocephalic and oculovestibular responses Extensor or flexor posturing Ataxic breathing (pontomedullary damage)

*Slow eye movement down followed by rapid return up to the mid plane. †Rapid eye movement up followed by slow return down to the to the mid plane

Table 3: **Neurological findings that help to localise site of structural brain disease by location of lesion**

and structural brain disease, are the least helpful with localisation.[4] Midbrain and pontine lesions can cause central neurogenic hyperventilation. Pontine lesions can cause cluster breathing (brief episodes of tachypnoea punctuated with brief spells of apnoea). Lower pontine and medullary lesions can produce ataxic breathing or apnoea.[2,4] Sighs or yawns can herald a decrease in level of consciousness resulting from rapidly increasing intracranial pressure.[28]

Fundoscopy can reveal subhyaloid haemorrhages (in subarachnoid haemorrhage or asphyxia) or papilloedema (increased intracranial pressure or severe hypertensive crisis causing posterior reversible encephalopathy syndrome).[4] The presence of venous pulsations suggests normal intracranial pressure but their absence is less useful.[29–32] Ocular ultrasonography of the optic nerve sheath with a high-frequency probe is reported to estimate intracranial pressure accurately.[33–36] This method could be a non-invasive way to detect raised intracranial pressure, allowing earlier and more rational therapeutic interventions, but validation is needed.

Combinations of physical findings characterise herniation syndromes (table 4) and their dynamic changes can be used to recognise progression of mass effect. Uncal (transtentorial) herniation classically presents with a dilated pupil ipsilateral to the compressive lesion (ipsilateral third nerve damage) with contralateral hemiplegia (ipsilateral cerebral peduncle compression causing contralateral motor findings). However, either component can be reversed. In up to 10% of cases, the dilated pupil is contralateral (falsely localising).[28,37] Because of the Kernohan notch phenomenon (contralateral cerebral peduncle compression), weakness ipsilateral to the lesion can also be falsely localising.[28,38] Although increased access to CT has diminished the influence of these false localising signs, they might still be relevant in hospitals without CT availability, especially if the treating physician is contemplating burr hole trephination. An awake, alert patient with a dilated pupil is very unlikely to have uncal herniation as a cause of the anisocoria.[28,39] Sixth nerve palsy from high or low intracranial pressure is also non-localising.

If progressive neurological disease associated with mass effect goes untreated, brainstem reflexes might fail in a caudal direction. Fixed pupils (midbrain) are followed by disappearance of corneal reflexes and oculocephalic responses (pons), followed by loss of cough response, apnoea, and loss of vascular tone (medulla).[3,4,17,28]

Combinations of physical findings can also characterise toxic syndromes. Pinpoint pupils with hypoventilation suggest opioids. Hypertension, tachycardia, and vertical or rotatory nystagmus suggest a dissociative agent, such as ketamine or phencyclidine. Increased salivation, lacrimation, bronchial secretions, diaphoresis, and incontinence suggest cholinergic agents. Sedative-hypnotic toxicity produces more varied symptoms, including normal vital signs (benzodiazepines), apnoea and circulatory collapse (barbiturates), and seizures (γ-hydroxybutyrate).

Laboratory testing

The initial assessment of comatose patients generally includes measurement of serum glucose, complete blood count including platelets, measurement of coagulation factors, electrolytes, renal, liver, and thyroid function, serum ammonia, and venous blood gas (table 2).[40] Co-oximetry should be included if carbon monoxide poisoning or methaemogobinaemia is suspected. Reliance on serum ammonia to diagnose hepatic encephalopathy is controversial because a single value is neither sensitive nor specific.[41,42] High ammonia concentrations can also occur with valproate-induced encephalopathy and rare deficiencies of urea cycle enzymes.[43] Blood should be cultured if infection is suspected. The value of toxicological testing for ethanol and drugs of abuse is questionable, and poisoning remains a clinical diagnosis. Routine toxicological testing rarely changes acute management.[44]

In patients with metabolic acidosis, a widened anion gap suggests one of four mechanisms (ketones, uraemia, lactate, toxins). Ketosis can occur in diabetes, alcohol misuse, or starvation. Uraemia generally produces acidosis only in later stages. Lactataemia can occur in sepsis, hypoperfusion, or Wernicke's encephalopathy,[45] or with toxins such as cyanide. Toxins can also produce acidosis by other mechanisms (carboxylic acid derivatives in ingestion of methanol or ethylene glycol, pyroglutamic acid in massive ingestion of paracetamol) or a combination of mechanisms (salicylates).

Brain CT

Not every comatose patient without a history of trauma needs brain CT. In three large series of patients presenting to emergency departments with non-traumatic coma, 42–58% had CT in the emergency department.[46–48] In the largest of these studies,[47] CT was done on 42% of 875 comatose patients. Of 633 patients ultimately diagnosed with a metabolic cause of coma, 151 (23%) had CT (abnormal in 4·6%); of 242 who proved to have a structural cause, 217 (90%) had CT (abnormal in 84%).

Examples of patients who do not need CT include hypoglycaemic patients who respond to dextrose, those with diabetic ketoacidosis, and patients admitted from nursing homes with fever and infected urine. Each group has a very likely diagnosis associated with diffuse neuronal dysfunction. Because some patients with early central herniation (table 4) can be confused with patients with diffuse neuronal dysfunction, continuous monitoring of comatose patients is crucial; failure to improve as expected should trigger diagnostic reassessment and CT.[28]

Brain imaging should be done without delay in comatose patients with unclear diagnoses, those for whom clinical asessment suggests structural injury, and those with preceding head trauma. The mode of imaging is generally CT because it is widely available and takes only seconds but if MRI is equally available, it has advantages over CT. The images must be interpreted in the clinical context. CT images can be truly positive (intracranial haemorrhage with shift), truly negative (normal scan in a poisoned patient), falsely positive (a unilateral frontal lobe mass without shift or mass effect), or falsely negative (normal scan in a patient with basilar artery occlusion). The physician cannot properly interpret the CT result, especially a negative one, without taking account of the neurological examination. Physicians should specifically check the CT image of comatose patients for tissue shift, hydrocephalus, intracranial haemorrhage (including bilateral isodense subdural haematoma), obliteration of the basal cisterns, subtle thalamic abnormalities, and a hyperdense basilar artery (figures 4–7).

CT images that show diffuse brain oedema without mass lesion should prompt the physician to consider insertion of of a device to monitor intracranial pressure.

Diagnostic time-out and checklist for reversible causes

When the CT result is positive, consultation with a neurologist or neurosurgeon can help to distinguish true positive results from false ones and to decide on next diagnostic and therapeutic steps. For all other patients (those with negative CT or positive findings thought to be incidental), a diagnostic time-out explicitly designed to avoid missing any reversible causes of coma can help (figure 3). At this juncture, we suggest that the physician asks five questions.

***Panel:* Commonly used coma scores**

Glasgow Coma Scale

Eye opening
1=does not open eyes
2=opens eyes in response to noxious stimuli
3=opens eyes in response to voice
4=opens eyes spontaneously

Verbal output
1=makes no sounds
2=makes incomprehensible sounds
3=utters inappropriate words
4=confused and disoriented
5=speaks normally and oriented

Motor response (best)
1=makes no movements
2=extension to painful stimuli
3=abnormal flexion to painful stimuli
4=flexion/withdrawal to painful stimuli
5=localised to painful stimuli
6=obeys commands

Full outline of unresponsiveness (FOUR) score

Eye response
4=eyelids open or opened, tracking, or blinking to command
3=eyelids open but not tracking
2=eyelids closed but open to loud voice
1=eyelids closed but open to pain
0=eyelids remain closed with pain

Motor response
4=thumbs-up, fist, or peace sign
3=localising to pain
2=flexion response to pain
1=extension response to pain
0=no response to pain or generalised myoclonus status

Brainstem reflexes
4=pupil and corneal reflexes present
3=one pupil wide and fixed
2=pupil or corneal reflexes absent
1=pupil and corneal reflexes absent
0=absent pupil, corneal, and cough reflex

Respiration
4=not intubated, regular breathing pattern
3=not intubated, Cheyne-Stokes breathing pattern
2=not intubated, irregular breathing
1=breathes above ventilatory rate
0=breathes at ventilator rate or apnoea

Does the patient need MRI or vascular imaging?

CT can miss treatable cerebrovascular causes of coma including basilar artery occlusion, posterior reversible encephalopathy syndrome with or without reversible cerebral vasoconstriction syndrome, early thalamic and brainstem ischaemic stroke, and cerebral venous sinus thrombosis. The locked-in syndrome from pontine

	Physical findings	Comments
Subfalcine	Progressive decrease in level of consciousness, generally in patients with hemispheric deficits (eg, hemiparesis, ipsilateral forced gaze deviation)	Midline shifts of >5 mm are associated with drowsiness; increasing shift causes increasing changes in consciousness Pericallosal and callosomarginal arteries can be compressed against falx
Central	Fixed midposition pupils and variable motor responses Pontine reflexes usually remain intact	Caused by downward pressure on the thalamus, buckling the brainstem
Uncal transtentorial	Ipsilateral dilated pupil followed by contralateral paresis. Decreased consciousness due to thalamic pressure. Later, the contralateral pupil is affected	Caused by compression of the midbrain by the temporal uncus. The posterior cerebral artery can be compressed against the tentorium
Brainstem compression from infratentorial lesion	Bilateral miosis and loss of corneal and oculocephalic reflexes	Typically caused by a cerebellar mass. Specific reflexes lost will depend on location of lesion and amount of compression. Can be associated with obstructive hydrocephalus. Intrinsic brainstem disease can have similar physical findings
Tonsillar	Respiratory arrest with loss of medullary function (cough reflex)	

***Table 4*: Herniation syndromes**

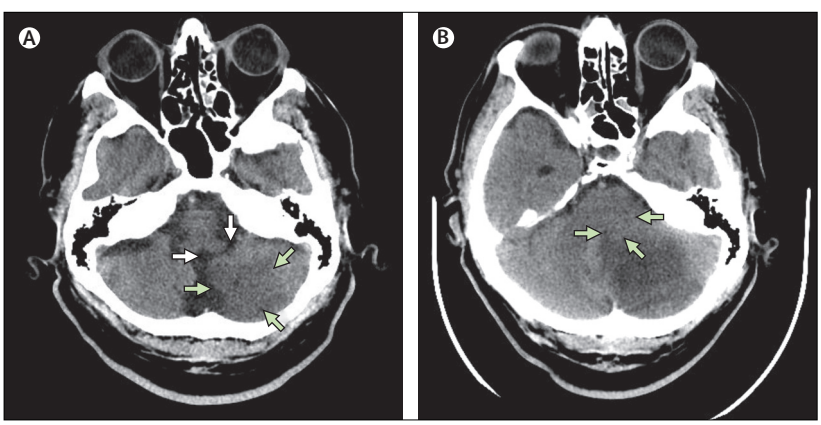

***Figure 4*: A 75-year-old man with diabetes and hypertension who presented with abrupt onset of dizziness and vomiting**
The vascular cause was a vertebral artery dissection. (A) first brain CT done after 8 h of symptom onset shows an acute infarction (green arrows). Note wide-open cerebrospinal fluid cistern between cerebellum and brainstem (white arrows). Over the next 2 days, he became increasingly somnolent. (B) CT 54 h after symptom onset. Note obliteration of previously open basal cisterns between swollen cerebellum and brainstem due to compression (green arrows).

damage, an embolic shower with several small cortical infarctions, and hypertensive encephalopathy should also be considered. Clinicians must consider whether a patient needs advanced imaging. Unless there is a likely specific diagnosis, vascular imaging (in most cases CT angiography) should be done expeditiously to exclude basilar occlusion. Such patients might have arm shaking mimicking seizure.[12] Many patients with posterior reversible encephalopathy syndrome report rapid onset of headache and visual symptoms and have seizures before consciousness decreases.[49,50] MRI typically shows edema manifested as bright signal on FLAIR and T2-weighted sequences, generally posteriorly. Even MRI can be falsely negative within the first 48 h of brainstem strokes, although infarctions large enough to cause coma might be more apparent.[51] Vascular imaging is necessary to diagnose basilar artery occlusion, vasoconstriction, and cerebral venous sinus thrombosis. Patients who have seizures with headache, especially with neurological deficits not localising to an arterial territory, should undergo non-invasive cerebral venography. Pregnant and post-partum women are at particular risk of many of these disorders.[52,53]

Does the patient need treatment for poisoning?

Poisoning is a common cause of coma. Of 938 consecutive patients with non-traumatic coma in one series, 352 (38%) had been poisoned.[54] Death was more likely in poisoned patients with low GCS scores than in those with higher scores.[55] Supportive care is the cornerstone of the management; however, in some types a specific therapy or antidote is beneficial. The relative frequency of various poisons differs geographically. The most common causes were pesticides in an Indian study of primarily rural patients,[56] ethanol in a Swedish study of comatose patients presenting to emergency departments,[54] and opioids and benzodiazepines in a series of patients admitted to an intensive care unit in Oman.[57]

Many toxins can produce coma directly or indirectly (table 1). We have not included toxins that generally lead to coma late in their course (such as heavy metals via cerebral oedema or multi-system organ dysfunction), or toxins that precipitate a separate, discrete cause of coma, such as α-amanitin mushrooms (producing hepatic failure and encephalopathy), toxins that only rarely cause coma (such as paracetamol in massive overdose), or agents that cause coma by cardiovascular collapse (such as most β blockers).

Does the patient need a lumbar puncture and intravenous antimicrobials?

Physicians must also include meningitis, encephalitis, and brain abscess in the differential diagnosis. For patients with possible meningitis who have decreased mental status, many experts recommend that CT be done before lumbar puncture.[58,59] CT might show a mass lesion associated with meningitis (infarction, hydrocephalus, subdural empyema, or brain abscess) although it is normal in most patients, even when the intracranial pressure is raised.[60] Other potential contraindications for lumbar puncture include coagulopathy or severe haemodynamic or respiratory

instability.[60] Some investigators[61] have questioned the logic of delaying lumbar puncture in patients with diminished consciousness but without focal findings. What is clear is that delays in antibiotic administration of as little as a few hours substantially increase mortality.[62,63]

If lumbar puncture is deferred or delayed for whatever reason, treatment must therefore not be delayed. Blood cultures should be obtained and intravenous dexamethasone and appropriate antimicrobials given immediately; after these steps, CT should be done followed by lumbar puncture once deemed clinically safe.[64] In comatose patients for whom CT does not show a contraindication to lumbar puncture, a small volume of CSF should be removed slowly through a small-gauge needle. If the patient has already been treated with antibiotics, blood cultures done before lumbar puncture will identify the pathogen in 50–70% of cases and various antigen and PCR tests will help identify a large proportion of the remainder.[60] If CT is deemed unnecessary, blood cultures should be obtained, the lumbar puncture done, and intravenous dexamethasone and antimicrobials given immediately after the lumbar puncture.

In cases of likely brain abscess or other mass lesion, lumbar puncture should be avoided because it can worsen tissue shifts.[65] Furthermore, the CSF rarely yields diagnostically important information in this group.[66–70] Encephalitis is another diagnosis that necessitates lumbar puncture. Encephalitis has many infectious causes.[69,71] Use of a simple flow sheet to guide clinicians in their assessment of CSF was shown to reduce errors in sample collection and processing and improve the diagnosis of viral encephalitis.[72] In a French series of 253 patients with encephalitis, herpes simplex virus accounted for half of cases; although cases due to bacterial infection were less common, the fatality rate was highest for these patients.[73] In an Indian series of 120 patients with acute febrile encephalopathy, causes included pyogenic meningitis (37%), viral encephalitis (28%), cerebral malaria (22%), sepsis-associated encephalopathy (9%), and tuberculosis (4%).[74]

Epidemiological context might suggest various diagnoses—tick exposure (anaplasmosis, babesiosis, rickettsiosis, and borreliosis), immunocompromised state (eg, *Listeria, Nocardia, Aspergillus, Cryptococcus,* or *Toxoplasma* species), and geography (neurocysticercosis, cerebral malaria).[69] Even the weather can have a role; an Indian study reported a surge in cases of cerebral malaria in the months after the monsoon.[74] For some patients with limbic or brainstem encephalitis, MRI is needed for diagnosis.

Septic patients can develop encephalopathy even in the absence of hypotension, hypoxia, or CNS infection. Neuronal dysfunction is probably due to increased vascular permeability and neuroinflammation.[75] Such patients can present with respiratory alkalosis that evolves to metabolic acidosis, an acid-base pattern also seen with salicylate poisoning. Renal or hepatic failure or other causes of diffuse neuronal dysfunction can also lead to confusion in these patients. Patients with hepatic failure might also be septic and have focal findings.[76] Sepsis can also precipitate coma due to other causes such as diabetic ketoacidosis and endocrinopathies.

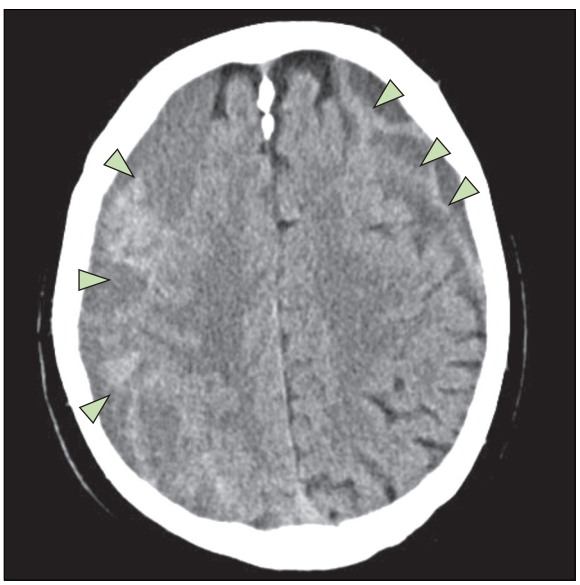

Figure 5: **An 83-year-old man with history of recurrent falls found unresponsive at home**
Non-contrast brain CT shows bilateral and partially isodense, especially on the right (left-hand side of the image) subdural haematomas (green arrowheads). He was treated effectively with urgent burr holes.

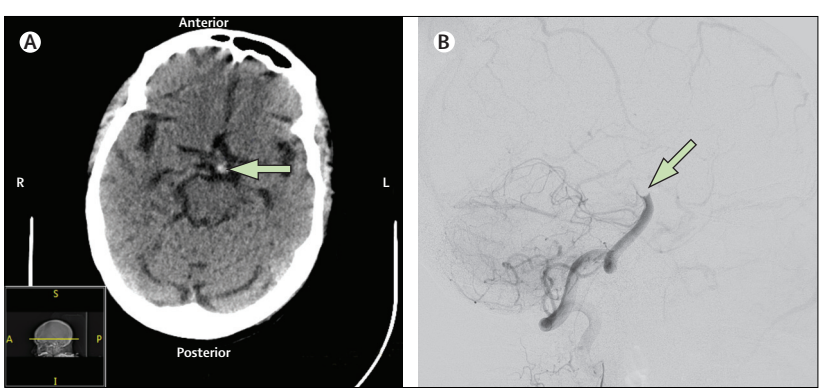

Figure 6: **Patient who presented with evolution of motor and oculomotor findings, then rapidly decreasing level of consciousness**
(A) Non-contrast brain CT shows a hyperdense basilar artery (green arrow). (B) Angiogram shows a cutoff at the distal basilar artery (green arrow).

Does the patient need an emergency EEG?

EEG has not been widely available in emergency departments. Emerging technology consisting of a portable device allows EEG testing on an emergency basis. Data are transmitted wirelessly and interpreted remotely.[77,78] However, the value of this technology still needs validation.[77,78]

Most studies on the value of EEG in emergency departments have been done in patients with a previous

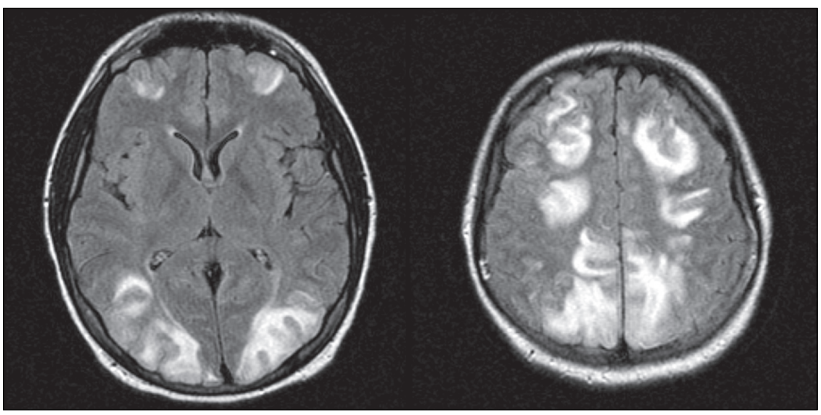

Figure 7: **A 38-year-old woman with eclampsia who presented with seizures and coma**
FLAIR images from MRI shows posterior reversible encephalopathy syndrome (white areas on the scans).

seizure or altered mental status and not specifically with unexplained coma. An EEG can confirm psychogenic unresponsiveness but this rare occurrence hardly justifies an emergency EEG. The EEG can also falsely suggest toxic-metabolic encephalopathy when a structural lesion is clear on MRI. However, patients who remain comatose after several generalised seizures might benefit from EEG to exclude non-convulsive status epilepticus, defined as prolonged seizure activity in the absence of major motor signs. Clinical clues to the presence of this disorder include nystagmus-like eye movements, myoclonic jerks, staring into space, lip smacking, chewing, and blinking.[79] Patients whose eyes are open but who are otherwise unresponsive can have non-convulsive status epilepticus.

Among comatose patients in intensive care, non-convulsive status epilepticus is not rare and patients with sepsis and brain anoxia are at increased risk.[80,81] Such patients with persistent unexplained altered level of consciousness should undergo EEG.[82] Three small series of emergency department patients with decreased level of consciousness reported rates of non-convulsive status epilepticus of 6–8%.[83–85] Elderly patients are at higher risk of misdiagnosed non-convulsive status epilepticus.[86]

Thus, EEG should be done in patients suspected of having non-convulsive or minimally symptomatic convulsive status epilepticus. It is especially important in patients intubated for convulsive status epilepticus because electrical seizures can persist even though paralytic or sedative drugs obscure their outward manifestations.

Does the patient need treatment of an endocrinopathy or thiamine replacement?

Endocrine disorders and thiamine deficiency are rare treatable causes of coma. Thyroid storm and myxoedema coma can both present with decreased consciousness.[87,88] Clues to the former include tachycardia, fever, and other previous symptoms of hyperthyroidism; clues to the latter are hypothermia, hypoglycaemia and previous symptoms of hypothyroidism. Sepsis can trigger both thyroid storm and myxoedema coma.[87–89] Although panhypopituitarism does not generally present with decreased consciousness, acute pituitary apoplexy (in most cases caused by haemorrhage into a previously undiagnosed adenoma) is a medical emergency that evolves rapidly.[90] Severe headache, varying degrees of ophthalmoplegia, and bitemporal hemianopsia precede or accompany the diminished consciousness.[90] CT might be diagnostic, but MRI is the imaging study of choice.[90] About 20% of patients with Addison's disease present with decreased level of consciousness.[91] Adrenal crisis causes circulatory collapse and is a medical emergency. Hypoglycaemia, bradycardia, and hypotension are clues to this diagnosis.

Thiamine deficiency is seen not only in malnourished alcoholic patients but also in those with cancer, previous bariatric surgery, or hyperemesis gravidarum.[92,93] Various combinations of acute encephalopathy with ataxia and ophthalmoplegia and lactic acidosis can occur.[45] When suspected, empirical treatment for these endocrinopathies and thiamine deficiency should be started without waiting for the results of laboratory tests.

Prognosis

In the earliest hours of care, the physician often does not have all the relevant information needed to give an accurate prognosis about comatose patients. Furthermore, various toxins, the locked-in syndrome, posterior reversible encephalopathy syndrome, severe Guillain-Barré syndrome, and hypothermia can mimic brain death.[94–97] For these reasons, one should be extremely cautious about predicting a patient's outcome early in the course, especially in the emergency department.

Conclusions

Use of an algorithmic approach to the comatose patient allows physicians to reach a specific diagnosis in most cases. Along with the history, a targeted physical examination helps identify the type of coma and better allows clinicians to interpret the diagnostic studies. The initial clinical asessment will commonly suggest a specific cause. If not, CT is generally the next diagnostic test. When the cause of coma remains unclear, a checklist approach should be used to avoid misdiagnosing treatable conditions such as basilar artery occlusion and other cerebrovascular causes, reversible toxicities, systemic and CNS infection, non-convulsive status epilepticus, and endocrinopathy and thiamine deficiency.

Contributors
JAE and EFMW conceived the project. JAE wrote the first draft. All authors edited several subsequent drafts.

Declaration of interests
JAE reviews medicolegal cases, some of which involve patients with coma. We declare that we have no competing interests.

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