Coma and altered consciousness

Clinical problems

Update 2012

Module Authors (Update 2012)

Tarek Sharshar
Department of Intensive Care Medicine, Raymond Poincaré Hospital, Garches, France

Nicolas Weiss
Neurological Intensive Care, Pitié-Salpètrie Hospital, Paris, France

Module Authors (first edition)

Roland Dietler/Roger Lussman/Eva-Maria Weiss-Guillet

Module Reviewers
Tom Bleck
Fabio S Taccone
Janice Zimmerman

Section Editor
Mauro Oddo
## Coma and altered consciousness

### Update 2012

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LEARNING OBJECTIVES

After studying this module on Coma and altered consciousness, you should be able to:

1. Recognise coma and altered consciousness using a brief neurological examination
2. Undertake early management of the patient with altered consciousness
3. Manage specific conditions causing altered consciousness
4. Develop a comprehensive care plan for patients with altered consciousness and prolonged ICU stay
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INTRODUCTION

Altered states of consciousness may be the cause or the result of acute or critical illness and are a common reason for admission to the emergency department (ED) and the intensive care unit (ICU). Neurological examination may be difficult to perform in patients with altered consciousness or who are poorly cooperative and routine tests, commonly used in awake patients, may not be easy to apply. This may limit the clinical decision-making process and diagnosis. Moreover, repeated neurological evaluation is necessary in patients with altered consciousness to detect complications of both extra-neurological and systemic diseases occurring in the ICU.

A structured, logical, and effective approach to manage patients with altered consciousness is required to diagnose, treat and prevent secondary damage to the brain or other organ systems. This needs a process of simultaneous evaluation and treatment.

Definitions

Consciousness is defined as a state of awareness of self and environment and the ability to respond to environmental factors. It can be divided into two closely interrelated components:

- **Arousal** (wakefulness, alertness, or vigilance) is clinically defined as the ability to open the eyes and the presence of sleep/wake cycles. Arousal is regulated and depends on the intact function of the Ascending Reticular Activating System (ARAS), a large sub-cortical area of the brain located in the brain-stem, the diencephalon (hypothalamus and thalami), the basal forebrain and the projections to the cerebral cortex – see ‘anatomical substratum’ below.

- **Awareness** (awareness of self and environment, i.e. the content of consciousness) is clinically defined as the ability to obey commands. It is regulated and depends on the intact function of cerebral cortex and its sub-cortical (mainly thalamic) connections.

Alteration of consciousness progresses from somnolence, i.e. lethargy, where the patient is drowsy but requires only moderate stimuli for arousal (once awake, the patient speaks and acts slowly, but otherwise normally) to stupor, where the patient can be partially awakened by strong external stimuli (but falls back into stupor as soon as the stimulus is removed) to the final stage represented by coma.

Coma is clinically defined by a state of unresponsiveness in which the patient does not open the eyes, does not follow commands, cannot be aroused, and has no awareness of self or environment.

Vegetative state (VS) is characterised by arousal without signs of awareness, a wakeful unconscious state. As stated by the Multi-Society Task Force for Persistent VS, this condition may be transient, marking a stage in the recovery from severe acute or chronic brain damage. Persistent VS is arbitrarily defined as VS present one month after initial brain injury, but it does not mean that it is irreversible. Permanent VS means irreversible and is defined by the Multi-Society Task Force for Persistent VS, as VS present at three months after a non-traumatic or at 12 months after a traumatic brain injury.
Minimally conscious state is characterised by the presence of inconsistent but reproducible goal-directed behaviours e.g. response to command, verbalisations, visual pursuit. The gold standard for detecting signs of consciousness is still behavioural assessment with detailed bedside neurological assessment that can be difficult in the ICU, because of tracheal intubation, tracheostomy or motor impairment. Standardised neurobehavioural assessment by the revised version of the coma recovery scale (CRS-R) has emerged as a valuable tool to minimise misdiagnosis.

Delirium is a fluctuating change in consciousness and awareness, mainly characterised by an alteration of attention and organisation of thinking associated with abnormal sleep–wake cycle, psychomotor activity, perceptions (e.g., hallucinations, illusions) and emotional behaviour.

Since coma is the most severe form of altered consciousness and is frequently life-threatening, this module will focus on its management.

**Anatomical substratum of arousal and awareness**

The ascending reticular activating system (ARAS), the primary arousal structure, is located in the upper pons and in the lower midbrain in the posterior part of the upper two-thirds of the brain-stem. A ventral pathway projects to the hypothalamus and to the basal forebrain; a dorsal pathway projects to the reticular nuclei of the thalamus; and a third pathway projects directly into the cortical regions. From the basal forebrain, two main bundles project diffusely to several cortical areas. The reticular nuclei of the thalamus connect to other nuclei in the thalamus. They are involved in a thalamo-cortical circuit that controls cortical activity. Some regions of the cerebral cortex may also make specific contributions to consciousness.

Efficient cortical arousal needs intact ARAS. Disorders are able to provoke coma either by a diffuse interference with this arousal system, e.g. metabolic brain dysfunctions, global cerebral ischaemia, or by interference with one or more strategic sites, e.g. brain-stem infarction. Focal lesions in the cerebral cortex are less likely to affect arousal.

Thus, the first approach to comatose patients consists, after initial stabilisation, in complete neurological assessment.
1/ HOW TO RECOGNISE AND ASSESS THE PATIENT WITH ALTERED CONSCIOUSNESS

Recognising a comatose patient

If the patient does not respond to voice or vigorous shaking, apply a noxious stimulus but it is important to minimise noxious stimuli whenever possible to avoid unnecessary suffering.

The comatose state is a life-threatening condition, therefore application of the ABC (Airway, Breathing, Circulation) algorithm and immediate treatment can be urgently needed before further assessment.

**Note** Performing a brief neurological examination before sedation administration for intubation or any other reason (e.g. agitation) is important.

Neurological assessment of comatose patients

Neurological examination of comatose patients is preceded by a general examination to reveal evidence of head trauma, meningeal irritation, purpura, elevated intracranial pressure or other diagnostic findings. Even though the neurological examination is modified by sedatives, it remains informative in patients who have been given sedative or analgesic agents. Subtle myoclonus particularly of the eyelids should be sought; this sign may suggest seizures.

Neurological examination should at least include examination of (1) the best motor responses to noxious stimuli, (2) brain-stem reflexes, (3) respiratory pattern and (4) reflexes.

(1) Best motor responses

The recommended noxious stimuli are pressure to: the supraorbital ridge, the nail beds of the fingers and the toes, the sternum and the temporomandibular joints. Spontaneous, purposeful or non-purposeful movements, withdrawal or posturing reflexes, including any evidence of lateralisation of signs, to noxious stimuli are noted. Eye opening, if not present to voice or spontaneously, in response to the noxious stimulus is also noted.

(2) Brain-stem reflexes

Brain-stem reflexes testing should at least include pupillary responses and ocular motility. Ocular motility can easily be tested by holding eyelids opened to observe eye position and movements. Most comatose patients have only a slight exophoria, so position of both eyes should be conjugate. Disconjugate eye positions suggest the presence of a brain-stem lesion. Vestibulo-ocular responses tested by lateral head movement (‘doll’s eyes manoeuvre’) may be used to elicit eye movements if they are not present spontaneously, but should be avoided if a fracture or dislocation of the cervical spine is possible. In these cases, cold caloric testing is preferred, provided that the tympanic membrane is intact. Corneal reflex testing is rapid and may have a
major prognostic value. Tracheal suctioning in mechanically ventilated patients allows testing of the cough reflex.

See the ‘status of pupils’ image in the PACT module on Traumatic brain injury.

(3) Respiratory pattern

The pattern of respiration helps to determine both the level of brain damage and the cause of coma (Cheyne–Stokes, bradypnoea, apneustic breathing, ataxic breathing). However, the need for stabilising vital functions and the urgent need for mechanical ventilation may decrease their value. For more information see Plum and Posner.


THINK: The evaluation of the respiratory pattern may provide clues to the cause of the coma and of the localisation of the brain pathology. However, this is not highly specific.

Q. What does deep and rapid regular breathing, also called Kussmaul breathing, suggest as possible cause of coma?

A. This classic breathing pattern suggests a metabolic origin of coma, such as diabetic ketoacidosis or other severe cause of metabolic acidosis.

See also the PACT module on Electrolytes and Homeostasis.

(4) Reflexes

Examination of deep tendon reflexes and plantar responses can be informative particularly when lateralisation of pathology is suggested.

Standardised assessment and follow-up

Neurological assessment of comatose patients should be reproducible and standardised to follow neurological evolution. The bedside detailed neurological examination of coma should be assessed by validated scales.

- The Glasgow Coma Scale (GCS) remains the most widely used coma assessment scale. First, GCS may not always be reliable in mechanically ventilated patients, particularly with regard to the verbal component. Second, GCS lacks assessment of an important component of coma assessment in ICU patients, i.e. testing of brain-stem reflexes.

See GCS scoring in the Traumatic brain injury module Task 1.

- The Full Outline of UnResponsiveness score (FOUR) is a relatively new coma assessment scale that includes brain-stem reflexes. It tests four components of brain function (eye response, motor response, brain-stem reflexes, and respiration pattern) and it has been validated in mechanically ventilated ICU
patients. Other scales, e.g. the Glasgow–Liège Scale, the Reaction Level Scale-85 or the Innsbruck Coma Scale, that included brain-stem reflexes testing have been proposed but have never gained wide acceptance.

---

**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

**Brain-stem 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 ventilator rate  
0 = breathes at ventilator rate or apnoea

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719522/


Patient evaluation and treatment must occur simultaneously in order to prevent secondary brain injury.

Q. The Glasgow Coma Scale is a standard means of evaluating patients with altered consciousness. What physiological conditions must be fulfilled for the GCS to be reliable?

A. The result of GCS testing is only reliable when the patient is stable i.e. in the absence of hypotension and/or hypoxaemia.

Q. Drugs used in the acute/critical care circumstances influence the GCS. Outline two categories of such drugs and their effects on the GCS.

A. 1. Sedatives, and even intense analgesia (with opiate drugs), may decrease the GCS.

2. Neuromuscular blocking agents (in ventilated patients) are particularly relevant as they invalidate the GCS completely.

Q. The GCS examination includes evaluation of the patient’s response to verbal commands or painful stimuli (eye opening, verbal response, motor response). Why is it important to check the patient’s ability to open their eyes when they have no motor response to painful stimuli?

A. Using the GCS you can check various neurologic systems or pathways. Patients with severe brain–stem stroke can evolve to a locked-in syndrome. They are not able to perform a verbal or a motor response and the only way these patients can react is to open or move their eyes.

Q. Is the same true for any acute, non-stroke, neurological diseases/conditions?

A. Yes, the same is true for severe forms of the acute inflammatory demyelinating neuropathy, Guillain-Barré syndrome. However, these patients may (rarely) lose the ability to open their eyes as well; electroencephalography may be the only way to determine that they are conscious.
2/ EARLY MANAGEMENT OF THE PATIENT WITH ALTERED CONSCIOUSNESS

Early management of the comatose patient

All alterations in arousal are acute life-threatening emergencies. Therefore apply the ABC algorithm and perform immediate treatment as needed.

PACT modules on Clinical examination, Airway management, Hypotension, Multiple trauma – Task 1 primary assessment.

Airway

Evaluate airway and protect the cervical spine, if there is a suspicion of possible cervical spine injury. Assume and check for signs of upper airway obstruction and open airway; administer oxygen immediately. Check the oxygen saturation by pulse oximetry. If ventilation remains inadequate despite clearing the upper airway by suctioning, perform mask ventilation and proceed to tracheal intubation.

![Warning]

Hypoxia is the number one killer, and hypoxia with hypotension is the main cause of secondary brain injury.

Q. Why do patients with a Glasgow Coma Scale score equal to or less than 8 points need intubation?

A. A Glasgow Coma Scale score equal to or less than 8 indicates deep coma with probable loss of protective reflexes such as swallowing, coughing, and the ability to maintain a clear airway.

Q. Give another reason for intubating patients with a GCS ≤8?

A. Because of the risk of hypoventilation, which may elevate PaCO₂ and so may exacerbate intracranial hypertension.

![Warning]

Always remember that the cervical spine could be injured due to accident or fall during loss of consciousness.

Breathing

Use inspection, palpation, percussion and auscultation to rule out or confirm any pathology that may interfere with oxygenation and/or ventilation, such as pneumothorax, haemothorax or flail chest. If there is any relevant pathology it should be treated before proceeding to an assessment of the circulation.
**Circulation**

Hypotension is a major cause of secondary brain injury. While awaiting final diagnosis of coma, mean arterial pressure should be maintained at least >70 mmHg in an attempt to ensure adequate cerebral perfusion pressure.

Isotonic saline is a suitable solution to restore circulating volume. A systolic arterial pressure equal to or higher than 100 mmHg is adequate and safe for most patients.

While obtaining venous access, blood samples are collected for laboratory tests (see below).

**Note** Severe hypotension itself can cause loss of consciousness, even in the absence of primary cerebral pathology.

**Volume resuscitation**

All comatose patients should receive isotonic solutions for resuscitation, preferably normal saline. An exception to this rule is the bolus administration of glucose to hypoglycaemic patients.

**Disability/other acute considerations**

**Hypoglycaemia**

Hypoglycaemic coma is common and the benefits of immediate administration of glucose outweigh the theoretical risks of additional harm to the brain if hyperglycaemic, hyperosmolar or anoxic coma is the underlying pathology.

If there is no immediately available blood glucose testing (fingerstick glucose or quick stat lab blood glucose) a 25G bolus of glucose (50 mL glucose 50% i.v. push) should be given without waiting for confirmation of hypoglycaemia.

**Warning** Thiamine must be given before the glucose infusion to prevent Wernicke’s encephalopathy in malnourished, thiamine-depleted patients.

**Seizures**

Repeated generalised seizures damage the brain and must be terminated as soon as possible. Initial treatment is with intravenous benzodiazepines; lorazepam is currently considered to be the agent of choice.

**Patient history**

After the life-saving ABC, collect further information from the paramedics, police, bystanders, relatives, or friends. Relevant information is important and can help you narrow your differential diagnosis and rationally order your diagnostic steps. The history should include the following:
• Was a witness present?
• The onset of comatose state? (sudden or rapidly progressive onset)
• Accompanying complaints? (headache, thunderclap headache, vomiting, fever, seizures)
• General medical history (including psychiatric history)
• Recent medical history (surgical procedures, infections, current medication)
• Presence of empty medicine bottles or access to drugs (illicit drugs, sedatives, narcotics, psychotropic drugs).


Any evidence for structural coma?

Coma results from either a diffuse interference with the arousal system or localised interference with one or more strategic sites, especially the ARAS. Thus, for the early management of coma, it is helpful to divide the causes into two broad categories:

• Structural (e.g. brain-stem infarction, bilateral large damage of the hemispheres)
• Non-structural (e.g. metabolic or toxic brain dysfunction, global cerebral ischaemia)

Classically, patients with structural coma have focal neurological deficits (unilaterally dilated, non-reactive pupils, asymmetric motor responses, disconjugate ocular movements). Patients with non-structural coma more commonly have reactive pupils and absence of focal neurological deficits. An important exception to this rule is the relatively common presence of focal neurologic findings in hypoglycaemic patients; thus, one must always ensure that the patient has an adequate glucose concentration. In addition, patients with seizures of focal origin may have a post-ictal paresis (Todd’s paresis) that may raise the question of an acute cortical lesion.

For the causes of coma see the table below, and references:


[9]
### Structural coma

**Vascular**
- Vertebrobasilar strokes, bilateral diencephalic infarcts
- Bilateral cortical or sub-cortical infarcts
- Occlusion of vessel supplying both hemispheres

**Infective** with mass effect
- Abscess, subdural empyema

**Neoplastic**
- Primary or metastatic

**Trauma**
- Haemorrhagic contusions, oedema, haematoma

**Increased intracranial pressure**
- Reduces cerebral blood flow

### Non-structural coma (toxic or metabolic coma)

**Electrolyte imbalance**
- Hypo- or hypernatraemia, hypercalcaemia, hypophosphataemia, severe hypomagnesaemia

**Endocrine disorders**
- Hypoglycaemia, non-ketotic hyperosmolar state, diabetic ketoacidosis, myxoedema, Addison’s crisis

**Vascular**
- Vasculitis*, DIC*, hypertensive encephalopathy*, thrombotic thrombocytopenic purpura (TTP)*

**Toxic reaction**
- Ethanol, drug overdose, carbon monoxide (CO) poisoning, lead intoxication

**Severe infections**
- Meningitis*, encephalitis*, cerebral malaria. Infected devices e.g. shunts and encephalopathy due to systemic sepsis.

**Medication side effects**
- Reye’s syndrome, neuroleptic malignant syndrome, central anticholinergic syndrome, serotonin syndrome

**Deficiency states**
- Thiamine deficiency (Wernicke), niacin deficiency (pellagra)

**Organ failure**
- Uraemia, hypoxaemia, hepatic encephalopathy*, Hypoxic-ischaemic encephalopathy (HIE) – post-resuscitation from cardiac arrest, CO₂ narcosis

**Epileptic**
- Status epilepticus (incl. non-convulsive status), post-ictal state

**Hypothermia and hyperthermia**

**Psychogenic coma**

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* can also lead to structural coma
For the next ten patients entering the ICU with the diagnosis of coma, classify the cause of the coma into structural or non-structural according to the above table. For cases of non-structural coma, try to find the pathophysiologic explanation for the coma.

**Q. Do all patients with altered consciousness need ICU treatment?**

A. No but regardless of the nature of the cause of altered consciousness, patients with altered consciousness need close and constant surveillance to detect a further deterioration in the level of consciousness. Prediction of the clinical course is inexact and close surveillance can normally only be guaranteed in a critical care environment.

**Q. What are the criteria for ICU admission in patients with altered consciousness?**

A. Admission to the ICU depends also on the severity of the disturbance of the consciousness e.g. a GCS of 8 or less normally warrants tracheal intubation but, even when coma is less severe, a deteriorating state of consciousness provides additional evidence for critical care admission.


See also the PACT module on Electrolytes and Homeostasis.

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**Anecdote** An intubated and sedated 30-year-old patient was transferred to the ICU after a scheduled operation for a brain tumour. The plan was to allow him to wake up and then wean him from the ventilator, but when the sedation was stopped the patient did not wake up.

Despite being given drugs to antagonise the sedatives, the patient had no motor reaction and absent corneal reflexes; only tachycardia and arterial hypertension were noted.

A neurological examination revealed absent muscle reflexes. A nerve stimulator placed at his forearm showed profound neuromuscular blockade. He was re-sedated.

Review of the anaesthetic technique showed a calculation error for the neuromuscular blocking drug, which had been given continuously via a syringe pump. After appearance of one twitch in the train of four stimulating mode, the neuromuscular blockade was reversed and the patient was able to move all extremities. Without a well-performed clinical evaluation and neurological examination, this situation could have led to numerous expensive investigations, including a computed tomography (CT) scan and potentially hazardous intra-hospital transport without any benefit.
Early specific treatment needed?

Patient evaluation and treatment must occur simultaneously. Some causes of coma need early specific treatment.

**Hypoglycaemic coma** is common and can be responsible for severe long-term neurological impairment. Blood glucose testing (fingerstick glucose or quick stat lab blood glucose) must be rapidly performed. In the case of low glucose level, i.v. glucose should rapidly be administered – see immediate (ABCD) measures above.

**Drug overdose** is the most common cause of coma presenting to Accident and Emergency Departments, being responsible for 30% of cases. If you have any suspicion of opioid or benzodiazepine overdose, you should assess and treat before proceeding to other investigations, unless the patient has traumatic brain injury or any other obvious explanation for coma. See the management of drug intoxication/poisoning in the PACT module on Major intoxication.

In case of **coma secondary to status epilepticus**, seizures should be terminated as soon as possible by i.v. anti-epileptic drugs. See above immediate (ABCD) measures.

In the case of **central nervous system (CNS) infections**, antimicrobial agents are urgently needed.

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**Diagnostic strategy**

Various diagnostic procedures are available to help the ICU physician evaluating the patient with altered consciousness. Which tests you use will depend on the clinical situation, but will probably comprise a combination of laboratory, radiology, electrophysiologic and cerebrospinal fluid (CSF) studies. What you choose depends on the history, the clinical situation, and the circumstances.

**Laboratory studies**

The differential diagnosis of altered consciousness is very broad. However, coma onset and the patient’s medical history, along with clinical examination and standard biological tests enable a diagnosis in most cases. Furthermore, some standard biological tests are helpful to diagnose potentially preventable causes of secondary systemic brain injury. Primary laboratory tests which are indicated in any comatose patients are given in the table.

Some more subtle biological tests should be considered according to clinical suspicion or hypothesis. It is common to assess serum ammonium level in every unexplained comatose state because of its therapeutic implication (control of increased cranial pressure).
Primary laboratory tests

<table>
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<tr>
<th>Test</th>
<th>Purpose</th>
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<tr>
<td>Electrolytes</td>
<td>Electrolyte imbalance: hyponatraemia, hypernatraemia, hypercalcaemia</td>
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<td>Blood glucose</td>
<td>Hypo or hyperglycaemia</td>
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<td>Complete leukocyte count with</td>
<td>Infective cause, sepsis</td>
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<tr>
<td>differential</td>
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<td>Liver enzymes</td>
<td>Hepatic encephalopathy</td>
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<td>Coagulation studies</td>
<td>Spontaneous intracranial bleeding, liver failure</td>
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<td>Creatinine and blood urea or urea</td>
<td>Renal failure</td>
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<tr>
<td>nitrogen (BUN)</td>
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<td>Arterial blood gas analysis</td>
<td>Hypoxia, CO₂ narcosis, acidosis, alkalosis</td>
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<td>Urine sample for toxicological</td>
<td>Benzodiazepines, opioids, tricyclic antidepressant agents, cocaine,</td>
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<td>screening</td>
<td>amphetamines, tetrahydrocannabinol (THC)</td>
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<td>Serum osmolality</td>
<td>Osmolal gap as clue to intoxication (ethanol, ethylene-glycol, methanol, isopropyl alcohol)</td>
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Secondary Laboratory Tests

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<tr>
<th>Test</th>
<th>Purpose</th>
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<tr>
<td>Thyroid studies</td>
<td>Myxoedema coma, thyroid storm</td>
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<td>Serum cortisol</td>
<td>Adrenocortical insufficiency (Addison’s crisis)</td>
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<td>Ammonia level</td>
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As clinically indicated

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<th>Test</th>
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<td>Cultures of blood and potential</td>
<td>Sepsis (septic encephalopathy)</td>
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<td>infected sites</td>
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Imaging

The availability of computed tomography has facilitated the diagnostic work-up of patients with altered consciousness. With a cerebral CT scan, the causes of structural coma are usually easily detected. Therefore a CT should be performed in every patient with a history of trauma, focal neurological deficit, sudden onset of headache or episodes of vomiting before the onset of coma. A CT scan should be performed first in any comatose patient, especially if focal neurological deficits are found during the initial core neurological

Always look at the CT or MRI yourself! You know best how it relates to the patient’s exam!
exam. MRI is more sensitive than CT but is cumbersome to perform in mechanically ventilated patients.

A neuroradiological examination is invariably required whenever coma (or any alteration of consciousness) remains unexplained.

**Lumbar puncture and cerebrospinal fluid analysis**

- A lumbar puncture is appropriate in any patient with a history of fever, neck stiffness or sudden severe headache.
- Examinations of cerebrospinal fluid (CSF) should include the CSF appearance, opening pressure, red blood cell count, white blood cell count and differential, glucose, protein, Gram stain, and cultures. Some extra fluid should be taken for special studies as indicated.

⚠️ Before a lumbar puncture is performed, if there is clinical suspicion of raised intracranial pressure (e.g. papilloedema, focal deficits), a CT brain scan should be performed to assess the risk of herniation.


⚠️ In patients with a high suspicion of bacterial meningitis or encephalitis, do not lose time performing a full diagnostic work-up (CT scan and lumbar puncture for CSF studies). Intravenous antibiotics must be initiated as soon as possible, particularly once blood cultures have been taken.

See the PACT module on Severe infection.

**Anecdote**

A 65-year-old female was transferred to the ICU from the emergency department because of altered consciousness: drowsiness, apathy, aphasia, and a GCS of 10 (M6; V2; E2).

The CT scan of the head was normal. Laboratory tests showed low serum-sodium concentration at 110 mmol/L. The history given by her husband revealed no relevant medical disorders other than chronic arterial hypertension and medication with an angiotensin receptor II antagonist in combination with thiazide diuretics. There was a gradual decline in consciousness with increasing fatigue over several days. A cerebrospinal fluid study performed because of nuchal rigidity was normal. The diagnostic work-up led to the diagnosis of a syndrome of inappropriate antidiuretic hormone (SIADH), probably induced by the medication. Therapy consisted of fluid/water restriction. Gradually the patient regained normal consciousness as the serum-sodium concentration normalised.
See the PACT module on Electrolytes and Homeostasis for more information on SIADH.

**Aetiological work-up according to coma (or delirium) associated signs**

<table>
<thead>
<tr>
<th>Clinical features associated with coma</th>
<th>Diagnostic strategy</th>
<th>Therapeutic strategy</th>
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<tbody>
<tr>
<td>Trauma</td>
<td>Brain imaging</td>
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<tr>
<td>Focal sign</td>
<td>Brain imaging</td>
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<tr>
<td>Seizure(s)</td>
<td>EEG and brain imaging</td>
<td>Discuss/start early antimicrobial agents</td>
</tr>
<tr>
<td>Fever</td>
<td>CSF, brain imaging</td>
<td></td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>CSF, brain imaging</td>
<td>Discuss/start early antimicrobial agents</td>
</tr>
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</table>

**Electroencephalogram**

Only by performing an electroencephalogram (EEG) is it possible to identify non-convulsive seizure activity as the cause of the coma. Towne and colleagues, in a retrospective study including a mixed general ICU cohort of comatose patients (n=236) in whom EEG was performed, found a prevalence of non-convulsive seizures of 8%, post-anoxic encephalopathy being the most common aetiology (42%). Other aetiologies included cerebrovascular accident (CVA) (22%), CNS infection (5%), traumatic brain injury (5%), metabolic encephalopathy (5%), alcohol or anti-epileptic drug (AED) withdrawal (5%) and tumour (5%).

Only one study focused on the prevalence of seizures in patients admitted to the ICU without a primary acute brain condition, in whom EEG was performed because of altered consciousness. Using a retrospective cohort of medical ICU patients (n=201) monitored with continuous EEG early after ICU admission (median 1 day) and for a median of 3 days, the investigators found a 10% frequency of seizures, of which 69% were purely non-convulsive. Sepsis (60%) and metabolic disorders (19%) were the two most common aetiologies. Severe sepsis was the only independent risk factor for seizures which in turn were strongly associated with a worse outcome. These findings reinforce the concept that septic encephalopathy, together with metabolic dysfunction (mainly, renal and hepatic failure) are risk factors for seizures. Thus, EEG is indicated in any ICU patients with persistent altered state of consciousness of unknown origin. Some specific EEG patterns can be suggestive of metabolic encephalopathy or herpes simplex virus encephalitis:

- Triphasic waves suggest metabolic or drug-induced encephalopathy.
- Diffuse slowing may indicate metabolic encephalopathy.
- Periodic lateralised epileptiform discharges suggest an acutely destructive process, such as herpes simplex virus encephalitis, brain abscess, or a rapidly growing neoplasm.
As aforementioned for neuroradiological examination, EEG is indispensable whenever a cause of the altered consciousness is not clear.


**Additional testing**

Additional tests should be performed if the above studies are negative or if there is a specific diagnostic hypothesis.

**Ammonia level**

Hyperammonaemic coma is rare except in association with hepatic encephalopathy. When liver disease is ruled out, hyperammonaemia should suggest the existence of a porto-systemic shunt or an inherited or acquired (e.g. valproate ingestion) urea cycle defect. Specific treatment of hyperammonaemia is urgently needed to prevent definite neurological impairment or death.

**Hormonal testing**

Thyroid studies and serum cortisol level are indicated if there is a clinical suspicion of myxoedema coma, thyroid storm or adrenal insufficiency or when no other cause is found.

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**For the next ten comatose patients, list the diagnostic tests performed. Decide which tests were used to confirm the diagnosis and which were used to exclude other possible causes. Were all the tests necessary?**

A patient with altered consciousness without a cause being identified should undergo brain imaging, EEG and CSF analysis.

**Reassessment of the comatose patient**

After performing the initial life-saving procedures, the comatose patient should be regularly re-assessed. This is best done by using a standardised score: the GCS with brain-stem reflex testing, or the FOUR score, which is well adapted to mechanically ventilated patients.

In many circumstances, these patients are given sedatives that modify brain-stem reflexes. However, neurological examination remains informative in sedated patients and this has been shown in non-neurosurgical, sedated critically ill patients (see Sharshar et al. CCM 2011).
In patients with brain injury, very high-dose sedatives are often necessary and may attenuate brain-stem responses or, in the case of neuromuscular blockade, abolish them entirely. In this case, direct or indirect monitoring of intracranial pressure is mandatory (see the PACT module on Traumatic brain injury).

In order to prevent secondary brain injury, the patient should be monitored for temperature, blood glucose level, blood sodium level, \( \text{PaCO}_2 \), \( \text{PaO}_2 \) and mean arterial pressure. Any unexpected change in neurological status should be investigated and neuroradiological, biological and EEG tests discussed.

For an overview see the following references.


**Triage**

Any patient with a suspected structural cause of coma should be immediately referred to a tertiary centre where neurosurgery, neurology, critical care and microbiology departments are available. Patients with a non-structural cause of coma should be referred to the intensive care unit for further evaluation, serial assessment, and specific and supportive treatment using a multidisciplinary approach.

**Rare causes of altered consciousness**

Sometimes, no definitive diagnosis can be made. In this case you will need to perform further investigations for rare causes of altered consciousness. These tests could include HIV serology (cryptococcal meningitis, toxoplasma encephalitis, primary CNS lymphoma), immunological work-up and auto-antibodies (e.g. rheumatoid factor, ANF antibodies, anti-DNA antibodies), tests for syphilis in blood and spinal fluid, and *Borrelia* serology. In any unexplained coma, MRI and neurophysiologic studies (EEG) must be done.

See below the flow chart for altered consciousness.
Initial drugs to be considered for administration before continuing work up
Thiamine 100 mg i.v. and glucose 50 ml 50% i.v. for every comatose patient

ABCs and mini neurologic exam

Laboratory studies (results need time)

Pin-point pupils
Respiratory depression
Coma: Naloxone 0.4 mg i.v.

Convulsions:
Lorazepam 0.1 mg/kg i.v.

Respiratory depression
Coma:
Flumazenil 0.5 mg i.v. titrated, if warranted

Reassessment and complete clinical exam

Conclusive? Yes
Specific treatment

No

Signs of increased ICP (fixed dilated pupil[s], rapid decrease in level of consciousness) or evidence of posterior fossa lesions (vomiting, ophthalmoplegia, multiple cranial nerve abnormalities)?

Yes
Mannitol 0.25-1 g/kg body weight i.v. If signs of brain herniation, recommended dose of mannitol is 0.5–1 g/kg

No
History

[18]
Biology
CT scan

Conclusive?
Yes → Specific treatment
No

Non-structural lesion likely or suspected, brain-stem lesion possible
Yes → Further investigations such as MRI, evoked potentials
No

Meningitis?
Yes → Lumbar puncture and CSF studies, antibiotics i.v.

Convulsions? Suspicion of non-convulsive seizures?

EEG

Conclusive?
Yes → Specific treatment
No

ICU treatment with multidisciplinary approach. Consider other causes
3/ ALTERED CONSCIOUSNESS – SOME SPECIFIC CAUSATIVE CONDITIONS

For details of the approach to and pathophysiology of these various conditions, follow the recommended links or consult the relevant PACT module.

Drug intoxication/poisoning

Intensivists are often confronted with intoxicated patients. There are a variety of causes, ranging from accidental exposure and medication overdoses to suicide attempts and illicit drug abuse. In addition, trauma patients may present with drug intoxication. Most of the intoxicated patients you will see are initially unconscious or have altered consciousness, so it is hard to know which toxic substances are involved. Often, the illicit drug abuser uses multiple substances.

In order to find classic presentations or toxidromes you will need the patient’s history, and a thorough clinical examination including vital signs, pupillary findings, mental status and muscle tone. ECG, laboratory findings, as well as a urine sample for toxicological screening, can be helpful.

For this module it is intended to make reference to a limited number of common intoxications. The ones chosen have specific antidotes but this will not be the only therapy required. Many will also need supportive (particularly cardio-respiratory) therapy as well – especially if the antidote is contraindicated or has an adverse clinical effect. More detailed reviews can be found in the following references.

See also the PACT module on Major intoxication.


Alcohol

Clinical signs

Every fifth patient admitted to hospital is a chronic abuser of alcohol. These patients have a higher risk of complications such as traumatic brain injury, seizures, Wernicke’s encephalopathy, delirium, nosocomial pneumonia, sepsis, cardiac and surgical complications. In our experience, alcoholic patients can be difficult for physicians. Coma should not be automatically ascribed to intoxication and other causes of coma can be unrecognised. It is important also to determine why the patient has stopped drinking.


**Q. What are the characteristics of Wernicke’s encephalopathy?**

A. Wernicke’s encephalopathy is characterised by nystagmus and ophthalmoplegia, delirium (or even coma), and unsteadiness of stance or gait (this triad is present in only 16% of the patients). Hypothermia is classical. Brain MRI can be helpful but a normal result does not rule out the diagnosis. Often, the only confirmation for the diagnosis is the evidence of the response to the treatment (thiamine for five days).

Eye findings will improve within hours to days; ataxia and confusion improve in days to weeks. 80% of patients are left with a disabling memory impairment called Korsakoff’s syndrome. Estimated mortality is 17%.

**Coma due to water intoxication in beer drinkers**

Disorders of consciousness, sometimes with seizures or pyramidal signs, have been described in association with serum-sodium levels of 98 and 120 mmol per litre in beer drinkers. The hyponatraemia is attributed to dietary sodium deficiency, the absorption of large quantities of water and the possible role of inappropriate secretion of antidiuretic hormone. Neurological dysfunction usually resolves with treatment.


**Treatment**

Alcohol increases diuresis and metabolism, and the breakdown products lead to acidosis. In acute intoxication with alcohol, the patient should be treated for dehydration, hypothermia, and often for severe hypoglycaemia and hypomagnesaemia.

**Note** Before treating hypoglycaemia, administer thiamine. Vitamin B1 is necessary for metabolism of glucose, and the clinical signs of thiamine deficiency (Wernicke’s encephalopathy, beriberi) could get worse with the administration of glucose alone.
**Benzodiazepines**

**Clinical signs**

Depression of respiration accompanied by hypercarbia is the most frequent cause of death following benzodiazepine poisoning or overdose. Clinical examination reveals depressed level of consciousness and mild bradypnoea.

**Treatment**

Benzodiazepine intoxication can be quickly reversed by the administration of flumazenil intravenously. Administration of the flumazenil can precipitate seizures and should be avoided in patients with epilepsy or in those taking benzodiazepines chronically or in the case of poisoning with pro-epileptogenic drugs (tricyclic antidepressants).

**Opioids**

**Clinical signs**

Depression of respiration accompanied by hypercarbia is the most frequent cause of death following opioid misuse. Clinical examination reveals depressed level of consciousness, bradypnoea and miosis.

**Treatment**

Opioid intoxication can be quickly reversed by the administration of naloxone but needs to be titrated to effect to attenuate the acute adverse effects of rapid opiate reversal – see Q/A below. Consider both intravenous and subcutaneous because of the short half-life of naloxone but note that the combination of i.v. and s.c. naloxone is not used in the USA. If naloxone reverses the comatose state, it is possible to administer naloxone by continuous infusion or repeated boluses.

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Illicit drug abusers often have infectious diseases (HIV, hepatitis B, hepatitis C), which are acquired and spread through the sharing of needles. Be mindful of your own safety during clinical investigations and while placing intravascular catheters.

**Q.** The administration of specific antidotes in cases of suspected intoxication is not free of complications. What are some possible complications that may occur with administration of a benzodiazepine antagonist?

**A.** Administration of the benzodiazepine antagonist, flumazenil, can precipitate seizures.

**Q.** What is the recommended dose of flumazenil in the treatment of a benzodiazepine overdose?

**A.** Use flumazenil 0.5 mg (0.1 mg/mL) as an intravenous bolus injection in 0.1 mg increments. This can be repeated (maximum 2 mg) until the patient reacts to verbal stimuli.
Q. When is flumazenil contraindicated?

A. Use of flumazenil is contraindicated (relatively) in patients who chronically use benzodiazepines or when there is concomitant abuse of medication that decreases the seizure threshold -- because of the risk of inducing seizures.

Q. What are the adverse effects of acute opiate antagonism using naloxone in a chronic opiate abuser?

A. The opioid antagonist naloxone can provoke an acute withdrawal syndrome, a catecholamine 'storm' resulting in arterial hypertension, cardiac ischaemia and rarely pulmonary oedema.

Q. What is the recommended dosage regimen of naloxone in the treatment of an opiate overdose?

A. Use naloxone 0.1–2 mg by intravenous slow bolus injection. If you suspect opiate intoxication, give the minimum amount to establish reversal of depressed breathing and coma.

**Cocaine**

**Clinical signs**

Cocaine inhibits the central and peripheral reuptake of norepinephrine, serotonin, and dopamine with overstimulation of the sympathetic nervous system. Use of this drug can lead to tremors, dyskinesias, delirium, hallucinations, psychosis, mydriasis, tachycardia, hypertension, coronary and cerebral artery vasospasm, myocardial infarction, lethal arrhythmias, aortic dissection, cerebral ischaemic stroke or haemorrhage and seizures.


**Treatment**

Due to the short half-life and rapid absorption of cocaine, detoxification and elimination measures are inefficient. Symptomatic treatment is necessary to control the sympathetic nervous system hyperactivity. Treatment only with β-blockers is contraindicated because of a higher likelihood of cocaine-induced lethality resulting from α-adrenergic overstimulation.

**Synthetic drugs**

Quite a range of synthetic drugs is available, and often the drug abuser does not know exactly what he has taken.

Frequently used drugs are Ecstasy (methylenedioxymethamphetamine, or MDMA), liquid Ecstasy (gammahydroxybutyrate) and ‘Eve’ (3, 4-methylenedioxymethamphetamine, or MDEA).
Clinical signs

The drug-induced syndrome leads to tiredness, weakness, tremors, shivering, hyperthermia, hyperreflexia, hyperhydrosis, seizures, and coma. ‘Eve’ can lead to a life-threatening situation with hyperthermia, rhabdomyolysis, and acute liver, coagulopathy and renal failure.

Treatment

Treatment consists of rehydration, as well as anticonvulsive and antipyretic therapy with benzodiazepines and dantrolene if necessary.

Do not use haloperidol if these patients are agitated: it will decrease the seizure threshold.


Medications

Benzodiazepines – Suicidal intoxication is common and is often seen in combination with other substances. Flumazenil can be cautiously used to reverse the effects when no chronic benzodiazepine use or concomitant use of medication that decreases the seizure threshold is suspected; management is otherwise supportive.

Barbiturates – Since being replaced by benzodiazepines as the hypnotics of choice, barbiturates are rarely seen in connection with drug overdose.

For more details see the following reference.


See also the PACT module on Major intoxication.

Cerebrovascular disease

Cerebral ischaemia

Cerebral ischaemia is one of the most frequent diseases and is an important cause of long-term disability, with a great economic burden.
We differentiate between generalised lack of oxygen causing global cerebral ischaemia and focal cerebral ischaemia.

Global cerebral ischaemia is due to cardiac arrest, carbon monoxide poisoning, severe prolonged hypoglycaemia or severe prolonged hypotension/hypoxaemia.

Focal cerebral ischaemia alters consciousness only in some specific conditions:
- **Brain-stem stroke** secondary to basilar artery occlusion that compromises the oxygen supply of the ARAS
- **Malignant stroke** where secondary oedema provokes herniation
- **Cerebral venous thrombosis** where venous occlusion provokes increased intracranial pressure and/or seizures.

**Intracranial haemorrhages**

Intracranial haemorrhages, including intracerebral haemorrhage and subarachnoid haemorrhage (SAH) are major causes of coma. Coma onset is abrupt. Previous medical history (hypertension, anticoagulants, or antiplatelet agent) can suggest haemorrhage. SAH needs urgent specific management and supportive treatment.

For details about treatment, see the following references.


http://stroke.ahajournals.org/content/38/5/1655.long

Malignant hypertensive encephalopathy

See also the PACT module on Hypertension

It is a cause of posterior reversible encephalopathy syndrome (PRES), usually manifested by headaches, visual disturbances and seizures. Brain MRI diffusion is diagnostic and shows typical patterns of bilateral hyper-intensities, predominantly in posterior parieto-occipital regions, but that also may involve the brain-stem.


Cerebral infections

Central nervous system infections are mainly represented by meningitis, encephalitis and brain abscesses. They urgently require diagnosis and antimicrobial therapy.

Meningitis is the most common form of intracranial infection, and acute bacterial meningitis remains a significant cause of morbidity and mortality.

Besides infective encephalitis, about 20% of encephalitis cases are non-infective, mainly immune-mediated.

Epidemiological data concerning encephalitis are presented in:


http://cid.oxfordjournals.org/content/49/12/1838.long

For more details on pathophysiology, clinical features, treatment and complications, see the following reference.


See also the PACT modules on Severe infection, Sepsis and MODS, and Pyrexia.

**Status epilepticus**


Generalised convulsive status epilepticus (GCSE) is defined as sustained seizure activity lasting for more than 5 minutes or ≥ 2 episodes of convulsive seizures with persistent alteration of consciousness. About 25 per cent of cases occur in patients having known epilepsy. The majority of the patients have no epilepsy and seizures occur as a complication of brain tumours, infections, traumatic brain injury, metabolic disorders, illicit drug intake or cerebrovascular disease. In patients with known epilepsy, the most common precipitating factor is withdrawal from medication or noncompliance with the regimen. Status epilepticus may recur in 26% of patients and has a high (22%) mortality rate.

GCSE is a medical emergency and prompt treatment is needed to prevent serious outcome, i.e. death and major brain damage. Besides GCSE, clinically silent non-convulsive status epilepticus (NCSE) may occur, particularly in comatose neurological or neurosurgical ICU patients. NCSE is characterised by subtle (e.g. reduced GCS, nystagmus, eye or facial twitching) seizures. Timing of treatment of these conditions is largely unknown, but experts recommend rapid treatment.

NCSE may often follow GCSE, particularly in refractory form of GCSE and may explain about 10% of comatose states of unknown origin. An electroencephalogram should be rapidly obtained in all the patients with coma of unknown origin. Some subtle myoclonus can be detected by attentive observation of the patient, especially on eyelids.
A distinction should be drawn between seizures and epilepsy. Epilepsy is a chronic condition, and epileptic patients may have repeated seizures because of difficulty in controlling their epilepsy. Most patients who are admitted in the ICU for seizures do not have pre-existing epilepsy.

Examine the next five patients in your ICU with altered consciousness for signs of non-convulsive status epilepticus.

Pathophysiology

Seizures result from an imbalance between cerebral excitation and inhibition. The excitatory neurotransmitters (e.g., glutamate) control a variety of ion channels and second messenger systems. An excessively rapid hypersynchronous depolarisation, triggered by failed removal of glutamate from the extra-cellular space, can occur in trauma, hypoxia, ischaemia, and hypoglycaemia.

Cerebral inhibition is provided primarily by gamma-aminobutyric acid (GABA). A loss of normal inhibition occurs, for example, during withdrawal or in the presence of GABA antagonists.

For further information, see the following reference.


The recent algorithm of Rossetti and Lowenstein (see reference below) is frequently quoted and it includes the use of diazepam, lorazepam, phenytoin and phenobarbital, administered in a planned sequence. In recent years newer treatment options have been studied and although a thiopental infusion was accepted as third-line therapy, midazolam or propofol infusions are sometimes advocated with comparable results. Furthermore, in current clinical practice, levetiracetam appears to be utilised increasingly.


Valproic acid is recommended especially when status epilepticus is related to discontinuation of Valproic acid.

Q. Why is continuous monitoring by EEG necessary in patients with status epilepticus?

A. Intermittent recording of the EEG is associated with the risk of under- and overtreatment. It is very important to remember that 20–30% of patients treated for status epilepticus will continue to have EEG evidence of seizures without clinical manifestations; so-called subtle non-convulsive seizures! Continuous EEG monitoring is mandatory when status epilepticus is refractory to first and second line therapy and requires pharmacologic coma with midazolam, propofol or barbiturates.

Seizures

When a patient in the ICU has altered consciousness, seizure should be ruled out and EEG performed. Subtle myoclonus is highly suggestive (eyelids, fingers). Metabolic disorders, interruption of sedatives, especially of antibiotics (beta-lactams and renal failure), drug withdrawal, are the main causes of seizures in ICU patients.

Metabolic coma

A wide variety of metabolic disorders can be responsible for altered consciousness or coma. Many are very common in critically ill patients; often several occur in combination.

Electrolyte and water disorders

Electrolyte disorders, especially alterations in sodium and calcium, are common in critically ill patients and often have multifactorial causes such as renal failure, fluid therapy, diuretic drugs, and loss of various secretions and fluids. These electrolyte disorders can alter consciousness directly or through induced seizures and may result in increased morbidity and mortality. For further details see:


See also the PACT module on Electrolytes and Homeostasis.
**Hepatic failure**

Patients with hepatic failure have many possible reasons for altered consciousness. Often they are alcohol abusers, so withdrawal with delirium and seizures as well as Wernicke’s encephalopathy is common. With hypoglycaemia and hypotension, there can be an insufficient supply of glucose to the brain cells and low cerebral blood flow. Finally, acute renal failure due to hepatorenal syndrome can lead to uraemic encephalopathy (see below), electrolyte and water disturbances, and acidosis.

The main reason for altered mental status is hepatic encephalopathy, which has many causes:

- Portal-systemic shunts, toxic substances (usually nitrogenous substances from the intestine such as ammonia or short-chain fatty acids and manganese) bypass the liver and accumulate in the brain, where overall central nervous system functions are depressed.
- The neuroinhibitory substance gamma-aminobutyric acid (GABA) accumulates and the actions of benzodiazepine receptor agonists are augmented.
- The plasma levels of endogenous opiates are increased.


See also the PACT module on Acute hepatic failure.

**Uraemia**

The clinical course of uraemic encephalopathy is characterised by variability from day to day and is more severe when renal function deteriorates acutely. Epileptic and cognitive symptoms are among the most typical manifestations. Pathogenesis is again multifactorial:

- Endogenous guanidine compounds are increased and lead to a direct neurocytotoxic effect.
- Presynaptic calcium/potassium pumps are decreased, with a reduction of neurotransmission.

For more details about diagnoses, stages and treatment, see the following references and the PACT module on Acute renal failure (Acute Kidney Injury Part II).
Endocrine disorders

Patients with endocrinopathies are normally treated as outpatients, but if the patient decompensates, the situation can become life-threatening and may be accompanied by neurological symptoms and altered consciousness. Complications of diabetes mellitus are mainly associated with altered consciousness.

The main causes are:

- Hypoglycaemia
- Diabetic ketoacidosis
- Hyperosmolar diabetic coma
- Adrenal insufficiency
- Myxoedema coma
- Thyroid storm

For more details see the following reference:


See also the PACT module on Electrolytes and Homeostasis.

Delirium

Delirium is associated with high mortality and morbidity, increased length of mechanical ventilation and hospital stay but also with long-term cognitive decline. It dramatically increases the care burden of the critical care team, particularly the nurses. It will only be briefly discussed here.

Its pathophysiology is highly complex, but its main and final mechanism is disturbed cholinergic activity. Delirium is a fluctuating alteration of level of awareness with reduced ability to direct, focus, sustain and shift attention. It is also associated with altered organisation of thinking. Noteworthy, it is infrequently associated with agitation. Indeed, hypoactive delirium is highly frequent in elderly ICU patients. It can occur a short time after ICU admission (usually hours to a few days) and can remain over several days. Alteration of sleep–wake cycle, abnormal psychomotor activity (agitation or hypoactivity), perceptual (e.g. hallucinations, illusions) or emotional disturbances and dysarthria can occur. EEG abnormalities (generalised slowing of background activity) are frequent and an EEG should be done when a clear cause is not present or when seizures are suspected.
It may be assessed in ICU with specific tools and various specific scales have been established. The two most widely used are:

- The Confusion Assessment Method for the ICU (CAM-ICU)
- The Intensive Care Delirium Screening Checklist (ICDSC)


http://www.mc.vanderbilt.edu/icudelirium/assessment.html


See the PACT module on Sedation and analgesia.

**Risk factors**

The classical risk factors for delirium in the ED and ICU are:

- Age (more than 70 years)
- Previous history of psychiatric disease or cognitive impairment
- Visual or auditory impairment
- Alcohol, tobacco, drug or medication abuse or withdrawal
- Total dose of sedative drugs in ICU (benzodiazepines and opiates)
- Medication overdose, especially antibiotics
- Surgery (especially extracorporeal circulation)
- Infection or sepsis

These risk factors are often combined which requires that a careful and rigorous diagnostic approach is followed. Remember that urinary retention and faecal impaction can be responsible for delirium in elderly patients.

Mechanisms of increased morbidity and mortality: agitated or delirious patients may endanger themselves or the medical staff as a consequence of increased psychomotor activity. Thus, a patient’s own removal of catheters or orotracheal tube can be highly deleterious. Alteration of consciousness related to delirium per se or induced by prolonged sedation increases the risks of aspiration. It has been suggested that sympathetic overactivity might contribute to cardiopulmonary failure, hypoxia, and multiple organ failure. Furthermore, delirium seems to induce or accelerate cognitive decline.

**NOTE** Delirium tremens is a life-threatening situation with a high mortality, especially in postoperative, post-traumatic, or critically ill patients.
It is clearly established that detection of delirium is indispensable and its prevention and treatment are major issues of clinical importance and to research in intensive care medicine. For instance, the relationship between sedation and delirium remains under debate as well as which protocol and drugs better reduce the incidence of delirium. Keeping sedatives at the lowest dosage level possible (by carefully assessing sedation depth with appropriate scales), daily interruptions of sedation whenever possible, avoidance of prolonged unnecessary sedation and providing adequate analgesia are all important preventive strategies to reduce delirium.

Regarding pharmacologic treatment of delirium, haloperidol remains the first choice, although it has not been assessed in a large randomised clinical trial.


Sepsis and septic shock

A common and sometimes initial clinical manifestation of sepsis is alteration of consciousness ranging from delirium to coma, a condition termed sepsis associated encephalopathy. By definition, it is not due to a direct infection of the brain. Its mechanisms are highly complex, involving metabolic, inflammatory and haemodynamic mechanisms. Indeed, endothelial activation, microcirculatory dysfunction and alteration of the blood–brain barrier are components of the inflammatory process. Alteration of cerebral perfusion (cerebral flow, autoregulation) contributes to brain injury. Along with these processes, metabolic (dysglycaemia, renal failure, hepatic failure) and therapeutic factors (antibiotics) alter brain functioning.

Neuroimaging (CT and/or MRI) should be performed in the setting of focal neurological signs or severe encephalopathy. EEG is often abnormal. Cerebrospinal fluid should be analysed when meningitis is suspected.

There is no known specific therapy, but the encephalopathy reverses quickly with successful treatment of the sepsis. Preventive measures are the same as those used for ICU delirium, and sepsis associated encephalopathy is sometimes difficult to clearly distinguish from ICU delirium or critical illness encephalopathy.

See the PACT module on Sepsis and MODS.

See the flow chart ‘Management of delirium/agitation’ below.
Management of delirium/agitation

- Potentially life-threatening causes?
  - Pain or harmless situations such as full bladder?
  - Drug-induced delirium?
  - Electrolyte- or acid-base imbalance?
  - Metabolic disorders?
  - Central anticholinergic syndrome?

  No

  Possible drug withdrawal state?

  Yes

  Serious danger to self or others, or destruction of equipment

  Yes

  Thiopental or propofol and intubation

  No

  Specific treatment

  No

  Older patient and/or Postoperative (ECC) and/or Post-traumatic

  Yes

  1) Lorazepam 1-2 mg i.v. repeated and/or 2) Clonidine 50 μg bolus i.v., then 25-75 μg/hour by infusion

  No

  Non-specific treatment:
  - Frequent reorientation to time and place
  - Restore sleep-wake cycle with adequate lighting and calm
  - Mechanical restraint if danger due to overactivity
  - Contact with family members
  - Consistency of nursing staff, as far as possible
  - Administration of thiamine
  - Early mobilisation
The substances used to treat agitation can also cause delirium, and haloperidol decreases the seizure threshold, so be careful of withdrawal seizure.

Determine how many of the next ten patients in the ICU show one or more risk factors for developing delirium. Think about whether and how you can reduce these factors. How many of the patients already have signs of delirium and are being treated for this condition? Is it possible to optimise the treatment?
Predicting the likely clinical course, including brain death

Several situations with altered consciousness or unconsciousness can culminate in brain death. A confident diagnosis of death depends on defining the point at which these processes become irreversible.

Situations causing brain death

The commonest causes of brain-stem death are traumatic brain injuries, subarachnoid haemorrhage, intracerebral haematoma, global cerebral hypoxia, and brain ischaemia.

Most patients with traumatic brain injury or haemorrhage have a devastating initial clinical course, with distinctive primary intracranial lesions and rapid development of secondary lesions due to raised intracranial pressure, low cerebral blood flow, ischaemia, brain oedema, and herniation.

A smaller number of these patients have cerebral deterioration due to extracranial complications such as respiratory or circulatory failure.

In this context, the loss of pupillary light reflex, of cough reflex and of any motor activity (together with varying other features of herniation) are often the features which first raise the possibility of evolution to brain death in practice.


See also the PACT modules on Traumatic brain injury, Acute brain ischaemia and Organ donation and transplantation.

Q. By checking the oculocephalic reflex (doll’s eyes) you assess the integrity of which neuroanatomical structures?

A. The oculocephalic reflex (doll’s eyes) tests the integrity of cranial nerves III (n. oculomotorius), IV (n. trochlearis), VI (n. abducens), the vestibular system, the pons and midbrain (fasciculus longitudinalis medialis), and neck proprioception.

Prediction of outcome

At the time of initial resuscitation, prediction of outcome is only possible in devastating situations where no therapeutic options are possible. All other situations involving primary cerebral lesions can change dramatically due to the unforeseeable course of brain oedema, numerous potentially life-threatening complications, and the influence of other traumatic injuries. After a short time, if the clinical situation is
more stable, it may be possible to predict neurological outcome with greater accuracy. Occasionally the outcome will be better than expected originally.

Critical illness polyneuromyopathy can exaggerate neurological deficits in patients with coma, leading to unnecessary investigations and overly pessimistic prognoses. See the following reference for further information.


See PACT module on Neuromuscular conditions.

As a rule, the longer the coma persists, the less favourable the prognosis. The absence of brain-stem reflexes also predicts a poor outcome.

**Prognosis after cardiac arrest**

Prediction of outcome after cardiac arrest has focused mainly in predicting an outcome no better than a vegetative state or severe disability with total dependency at three to six months after arrest. The majority of available studies were however done before the use of hypothermia.

The absence of a pupillary reaction to light, a motor response no better than extensor posturing to noxious stimuli and the absence of corneal reflex at day 3 after arrest were all associated in different studies with poor outcome with no false positive rate before the use of hypothermia. Preliminary data suggest that this remains true even if the time for evaluation needs to be delayed in patients treated with therapeutic hypothermia. Other clinical signs that are predictive for poor outcome have been reported. Thus, the absence of eye movements at caloric vestibule ocular reflexes and the presence of myoclonic status epilepticus are associated with a poor outcome.

The bilateral absence of N20 response of somatosensory evoked potentials (SSEP) is one of the major predictors of poor outcome after cardiac arrest.

The prognostic value of the serum concentration of neuron specific enolase (NSE) is still a matter of debate. The cut-off value may differ in patients treated by therapeutic hypothermia.

Brain imaging, CT scan or MRI, are still evaluated in these patients but cannot be used to assess neurological outcome.

**Note** Most of these predictive factors have been assessed before the hypothermia era. To what extent hypothermia alters their predictiveness needs to be assessed.
Two recent studies performed in the hypothermic era by Rossetti et al. suggest that an unreactive EEG background was incompatible with good long-term neurological recovery (CPC 1–2) and was strongly associated with in-hospital mortality. Furthermore, the presence of at least two independent predictors from the following four entities (incomplete brain-stem reflexes, myoclonus, unreactive EEG, and absent cortical SSEP), accurately predicted poor long-term neurological recovery.

In comatose post-anoxic patients, predictors of nonawareness are available but not those for awareness. Thus, it is still difficult to distinguish between patients who will evolve from minimally conscious state (MCS) to a fully conscious state, from those who will remain in MCS.

Clinicians should be aware of post-anoxic myoclonus, a rare condition that can easily be misdiagnosed as myoclonic status epilepticus. Contrary to myoclonic status epilepticus which has been associated with poor outcome, post-anoxic myoclonus responds well to specific treatment. The diagnosis of this condition should preclude active medical treatment withdrawal (see Venot et al.).

For more information see:


http://circ.ahajournals.org/content/122/18_suppl_3/S768.long
For more information about prognostic factors in traumatic brain injury see the PACT module on Traumatic brain injury.

**NOTE** Communication with the relatives of a brain-injured patient is very important, and their desire for information about the outcome is understandable. Nevertheless, it is necessary to impress upon families that the comatose patient may or may not awaken, that even if the patient awakens s/he may have major sequelae that may or may not improve and that the recovery process can take months or years and is filled with uncertainty.

See also the PACT module on Communication.

**Q.** Despite a range of possible technical investigations, predicting the clinical course and outcome in comatose patients is very difficult. Outline the importance of communication to the relatives of these patients?

**A.** One of the most important factors in the management of these patients is the ability of the nurses and physicians to communicate, both with each other and with the relatives. On the one hand it is necessary to communicate the uncertainty of the prognosis and on the other hand it is very important not to give too optimistic a view of the prognosis. The relatives must cope with the situation and you best help by being honest.

For more information about the diagnosis of brain death, managing potential organ donors, and the specific role of the ICU team, see the PACT modules on Ethics and Organ donation and transplantation.

**Prolonged altered consciousness and ICU stay**

Patients presenting with coma or altered consciousness as their primary cause of admission are often unable to recover rapidly, having survived the initial life-threatening event. Altered consciousness due to unnecessarily deep and prolonged sedation contributes to delayed convalescence. These patients become the chronic critically ill. When ICU stay is prolonged by altered consciousness there may be a further decline in functional status due to the effects of bed rest and lack of exercise, drug administration, a catabolic state and nosocomial infections. With regard to long-term survival and functional outcome, these patients will probably suffer a variable degree of long-term disability. Therefore, the physician’s expertise and experience, nursing care, a complex physiotherapeutic and rehabilitation programme and family involvement are all important issues for maintaining and improving cerebral and other organ functions, preventing further damage and improving clinical outcome with a reasonable standard of quality of life.

**In the sedated patient in ICU, whenever possible, sedative drugs should be discontinued every day and the patient should be neurologically assessed.**

**After awaking, all patients should be evaluated by a neurological and a minimal neuropsychological examination.**
**THINK:** Is there a necessity for deep and prolonged sedation of a patient? If not, make sure sedation is stopped regularly in order to assess the patient’s neurological status and to facilitate the preventative measures outlined in the table below.

Think about use of a protocol.


See also the PACT modules on Sedation and analgesia and Clinical outcome.

**Complications and their prevention in the chronically critically ill with altered consciousness**

The variety and number of potential complications in the chronically ill patient is enormous (see table).

<table>
<thead>
<tr>
<th>Complications</th>
<th>Examples of prevention strategies</th>
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<tbody>
<tr>
<td><strong>Confusion/delirium</strong></td>
<td>Communication (e.g., orientation of the patient and their family, providing them with ongoing information, allowing patient and family decision-making, visiting practice based on the patient’s needs, minimising the number of personnel coming into contact with the patient, planning for daily activities) Allow sleep at night, natural lighting, dim light at night Effective pain management Early mobilisation Adequate treatment of primary cerebral or systemic diseases</td>
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<tr>
<td>- Psychological and environmental factors (pain, anxiety, depression, sleep deprivation, immobility, threatening and foreign environment, sensory deprivation and overload, social isolation)</td>
<td></td>
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<tr>
<td>- Primary cerebral or systemic diseases (head trauma, vascular encephalopathies, infectious causes, dementias, epileptic and post-ictal states, hypoaxaemia, congestive heart failure, sepsis, endocrine-metabolic disturbances, vitamin deficiencies)</td>
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<tr>
<td>- Narcotics</td>
<td>Using protocols for sedation which should help minimise oversedation Symptomatic therapy in withdrawal syndromes</td>
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<tr>
<td>- Sedative overdose</td>
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<tr>
<td>- Withdrawal syndromes</td>
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<tr>
<td>Pulmonary complications</td>
<td>Other nosocomial infections</td>
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<tr>
<td>- Atelectasis</td>
<td>- Catheter-related bloodstream infections</td>
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<td>- Nosocomial and ventilator-associated pneumonia</td>
<td>- Clostridium difficile colitis</td>
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<tr>
<td>Effective pain management</td>
<td>Removal of any vascular access if not absolutely necessary</td>
</tr>
<tr>
<td>For the awake patient: deep breathing, maintaining a sustained maximal inspiration, mobilisation, e.g. incentive spirometer for motivation</td>
<td>Careful indication and choice of the insertion site of a central venous catheter, rigorous insertion practice, regular surveillance under meticulous care</td>
</tr>
<tr>
<td>For the intubated patient/the patient with a decreased level of consciousness: frequent repositioning, chest physiotherapy, positive pressure ventilation/breathing</td>
<td>Avoidance of total parenteral nutrition where enteral nutrition may be feasible</td>
</tr>
<tr>
<td>Scrupulous oral hygiene and general standards of infection control</td>
<td>Restrictive use of antibiotics if not indicated clinically</td>
</tr>
<tr>
<td>Extubation as early as possible</td>
<td>Infection control measures to prevent cross-transmission</td>
</tr>
<tr>
<td></td>
<td>Avoidance of catheterisation when not strictly required</td>
</tr>
<tr>
<td></td>
<td>Catheterisation should be terminated as soon as possible</td>
</tr>
<tr>
<td></td>
<td>Meticulous oral hygiene</td>
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Preventing or at least minimising complications is undoubtedly cost-effective, but is a tremendous challenge for the whole critical care team, requiring an aggressive multidisciplinary approach to the development and monitoring of standards of care.

**Physiotherapy**

In an immobilised patient with decreased cognitive awareness and muscle wasting, impairment of joint motion and contracture may occur rapidly. The patient is at further risk for developing compression neuropathies and pressure ulcers when positions are maintained for a long time. A carefully adapted mattress, frequent changes of position, and proper bed position limit the incidence of the latter complications. The amount of exercise needed to prevent contractures is not known. Passive and active assistive motion exercises ten times a day are recommended, which the physiotherapist can provide in collaboration with the nurse and the family.

*Note* The most important therapeutic modality in physiotherapy is physical exercise and early mobilisation.


**Nutrition**

After evaluation of the patient’s nutritional condition, metabolic demands, and required total caloric intake, the optimal diet for the specific clinical condition should be established. Whenever possible, enteral feeding should be used in preference to parenteral nutrition and should be started as soon as possible, using post-pyloric or jejunostomy feeding if nasogastric is not feasible.

See also the PACT module on Nutrition.


Rehabilitation

Rehabilitation should begin early and should continue after discharge of the patient to the surgical or medical unit.

**The goal of rehabilitation medicine is the maximum restoration of functional ability within the individual limits imposed by the underlying illness and the physical and/or mental impairment.**


Communication as part of a management strategy

An interdisciplinary approach to patient care facilitates all aspects of patient care being addressed in the clinical plan. However, communication, collaboration and continuous exchange of information between clinicians, nurses, patients and their families, physiotherapists, nutritionists, social workers, and under certain circumstances a psychologist, are necessary to ensure high-quality patient care. Communication helps the ICU caregivers provide optimal care, facilitates family understanding of patient care issues, supports families who are facing tremendous emotional (and also often financial) burdens, clarifies the process and options involved in the discharge planning process, and, last but not least, reassures the patient.

**Communication is a continuous process** that begins with the arrival of the patient and family and ends (usually) with the patient's discharge.

See the PACT module on Communication.
SELF-ASSESSMENT

EDIC-style Type K

1. After a car accident a passenger is brought to the accident and emergency department with a severe head injury. No other injuries have been reported from the scene. At admission her GCS is 7, ABP 90/55, O₂ saturation 98% and the blood gas spontaneous breathing air reveals pO₂ 10.7 kPa, PCO₂ 4.9 kPa, pH 7.46 and HCO₃ 26 mmol/L. What will you do while still in the A&E department?
   A. Nothing, but leave for immediate CT scan of the brain
   B. Rapid intubation and controlled ventilation
   C. Lie patient head-down to place a central venous line through the internal jugular vein
   D. Give pre-emptive mannitol prior to transport

2. Consciousness is a state characterised by awareness of self and the ability to respond to external factors. It can be sub-divided into:
   A. Wakefulness
   B. Stupor
   C. Coma
   D. Somnolence

3. Characteristics of the vegetative state (VS) include:
   A. Arousal without awareness
   B. Being defined as persistent if present one month after initial brain injury
   C. No eye opening
   D. No swallow reflex

4. Delirium is characterised by:
   A. Changes in consciousness but not in awareness
   B. Disorganised thinking
   C. Fluctuating course
   D. Constant increased psychomotor activity

5. The recommended noxious stimulus to provoke a motor response in a patient with altered consciousness is:
   A. Pressure to the eye-bulb
   B. Deep pinprick in the abdominal area
   C. Forced pinching in the upper arm
   D. Pressure to the nail-bed of the finger

6. Brain-stem reflexes include:
   A. Vestibulo-ocular response
   B. Pupillary response
   C. Corneal reflex
   D. Cough reflex
7. The Glasgow coma score includes:
   A. Pupillary response to light
   B. Best verbal response
   C. A four point scale on best motor response
   D. A value from 0 (worst) to 15 (best)

8. Important primary laboratory tests in patients with unexplained comatose state include:
   A. Blood glucose
   B. Prothrombin time (PT) or INR
   C. Serum cortisol
   D. Serum osmolality

9. Wernicke’s encephalopathy is an uncommon form of coma. Its characteristics include:
   A. Nystagmus
   B. Hyperthermia
   C. History of unsteadiness
   D. Anisocoria

10. Recognised risk factors for developing delirium in the ICU include:
    A. Advanced age
    B. Visual or auditory impairment
    C. Major surgery
    D. COPD

EDIC-style Type A

11. The FOUR score for testing of altered consciousness (Full Outline of UnResponsiveness score) of ICU patients includes all of the following EXCEPT:
    A. Eye response
    B. Motor response
    C. Brain-stem reflexes
    D. Respiratory pattern
    E. Verbal response

12. The commoner causes of ‘non-structural’ coma/altered consciousness in ICU include the following EXCEPT:
    A. Hypoglycaemia
    B. Hyperglycaemia
    C. CO (carbon monoxide) poisoning
    D. Post-ictal state
    E. Hypertensive encephalopathy
13. Usual first-line diagnostic procedures in patients with coma or reduced consciousness include all EXCEPT:
   A. Electrolytes
   B. CT of cerebrum
   C. CSF analysis
   D. Hormonal analysis
   E. EEG

14. The primary arousal structure in the brain (the ascending reticular activating system) is found in the:
   A. Cerebellum
   B. Dominant frontal cortex
   C. Hypothalamus
   D. Upper part of the brain-stem
   E. Thalamus

15. A 21-year-old male biker is brought to the accident and emergency department after driving off the road. He is spontaneously breathing with 10 L oxygen on a facemask. At admission his BP is 95/45, pulse rate 115, SpO₂ 92%, RR 22 and GCS is 7. What will be your number one priority in this patient?
   A. Rapid cerebral CT scan
   B. X-ray of his chest
   C. Tracheal intubation and ventilation
   D. Infusion of 1000 mL crystalloid
   E. Administration of morphine i.v. in small doses

16. The most common cause of reduced consciousness and coma in patients admitted to the accident and emergency department is:
   A. Hypoglycaemic coma
   B. Coma secondary to seizures
   C. Drug overdose
   D. CO₂ intoxication in chronic respiratory failure
   E. Meningitis or other CNS infections

17. The following clinical signs would lead you to suspect cocaine overdose as the cause of coma with the exception of:
   A. Tremors
   B. Mydriasis
   C. Tachycardia
   D. Hypotension
   E. Arrhythmias
Self-assessment Answers

1. FTFF
2. TTTT
3. TTFF
4. FTTF
5. FFFT
6. TTTT
7. FTFF
8. TTFT
9. TFTF
10. TTTF
11. Correct: E
12. Correct: C
13. Correct: D
14. Correct: D
15. Correct: C
16. Correct: C
17. Correct: D
PATIENT CHALLENGES

You are called to the emergency department to evaluate a comatose patient who appears to be in his mid-20s and has just been brought from a police station by paramedics. You perform a quick clinical survey. The patient’s eyes are closed, there is no verbal response but he flexes in response to painful stimuli. There is anisocoria and the pupils show a delayed reaction to light. His breathing is noisy, with a frequency of 8 breaths/min. His heart rate is of 115 bpm and blood pressure of 145/80 mmHg. You note the odour of alcohol, several tattoos, cigarette burns on the fingers, scars and skin ulcers, thrombosed peripheral veins, and fresh injection marks.

Often, at the beginning of an emergency procedure, you will have only limited information especially if it is not possible to speak with the patient.

Q. What immediate action should be taken?

A. Begin ABC (Airway, Breathing, Circulation). A careful assessment of the patient is required to ensure adequate ventilation and oxygenation. Take the possibility of (partial) upper airway obstruction and protective airway reflexes into account. Check chest expansion, oxygenation and auscultate for breath sounds.

In view of the bradypnoea and partial upper airway obstruction, you initiate airway support by opening the mouth, performing the jaw thrust manoeuvre, and providing supplemental oxygen via bag-mask ventilation. To avoid neck extension, a colleague provides manual immobilisation until the cervical collar is fitted. With these manoeuvres, chest expansion and oxygenation improves (was 80%, now 97%) as measured by pulse oximetry.

Q. What is the patient’s Glasgow Coma Scale (GCS) score? Indicate how the score is compiled?

A. The GCS is 5 (Eyes: 1; Verbal: 1; Motor: 3).

Q. What does this score signify?

A. It means the patient is deeply comatose and has a severe brain insult.

Resuscitation of patient in coma
Emergency airway management
Diagnosis of acute neurological disturbances

Link to the PACT module on Airway management

After the patient is stabilised, you have time to elicit information from the paramedics. They report that the patient, well known at the police station as a substance abuser, had threatened two security guards with a beer bottle after they were called to remove him.
from a shopping centre. The man had been aggressive and, during a struggle with the guards, had fallen heavily to the floor. The police were called, and took the man to the station, where he was locked in a cell to dry out. Thirty minutes later, however, a guard observed that the man was shaking uncontrollably and did not respond to calls. The alerted paramedics found a comatose patient with a GCS of 6. Supplemental oxygen was given and venous access managed with difficulty since most of the peripheral veins were thrombosed due to drug injections. The patient was transported to your hospital.

Q. Knowing that the patient has a history of abusing alcohol and other drugs and that a drug overdose could, at least in part, explain the alteration in consciousness, would there be a possible advantage to giving antidotes? Explain your answer.

A. The patient is intoxicated and presents with fresh injection marks. If antagonisable drugs are playing a major role in the decreased level of consciousness, the use of antidotes may improve the level of consciousness sufficiently to provide acceptable airway protection.

Q. Unlike opioids and benzodiazepines, no specific antidote is available for cocaine or alcohol. Is there a possible disadvantage to acute pharmacological reversal of opiates and benzodiazepines?

A. Yes, agitation which could be hazardous to the patient and staff and convulsions are possible immediate consequences.

Q. Does the clinical scenario suggest another possible cause for the altered consciousness?

A. Yes, the anisocoria and the history of a heavy fall to the floor strongly suggest the possibility of an intracranial lesion.

If you decide to use antidotes, you should still be prepared for immediate intubation.

After considering the patient’s history, you administer 100 mg thiamine with 50 mL of 50% glucose intravenously while you await the blood glucose test – the near patient glucometer machine is non-functional. You then administer 0.4 to 2 mg naloxone and 0.2 to 1 mg flumazenil. You order blood analysis for electrolytes, liver and renal function, alcohol concentration and you collect a urine sample for toxicological screening.

Q. Why it is important to give this patient thiamine before administering glucose?

A. Chronic alcoholics, such as this patient, are often vitamin-depleted; it is therefore essential to give thiamine before administering glucose to prevent the development of Wernicke’s encephalopathy.
Q. Are there certain patient groups in whom the risk of flumazenil induced convulsions is increased?

A. Flumazenil may particularly induce seizures in patients with a pre-existing seizure disorder, benzodiazepine addiction, concomitant tricyclic antidepressant overdose or during major sedative-hypnotic drug withdrawal.

Q. Flumazenil was therefore ill-advised in this patient. Is there a further reason why this was so?

A. If seizures occurred, benzodiazepines might no longer be effective as anticonvulsant therapy because benzodiazepine receptors are blocked.

The patient’s GCS score does not improve in response to the administration of antidotes. Heart rate and blood pressure are increasing, and the pupils begin to dilate. You proceed with intubation. The patient develops a generalised, tonic-clonic seizure and vomits repeatedly.

Aetiology of seizures
Withdrawal syndromes

Q. Other than the antidotes, what are other possible causes for these convulsions?

A. Another cause may be an intracerebral injury with contusions and/or epidural, subdural or subarachnoid bleeding.

Link to PACT module on Traumatic brain injury

Based on a new rapid deterioration in the patient’s oxygenation and a clinically evident new onset of bronchospasm, you suspect aspiration of gastric contents.

Note Don’t forget that there could be future ventilation problems because of the aspiration.

Q. Describe the possible impact of this complication on the clinical respiratory course.

A. Aspiration of gastric contents may lead to acute respiratory distress syndrome (ARDS – mild, moderate or severe), which may require prolonged mechanical ventilation and can cause significant morbidity and mortality.

Q. Describe the neurological consequences.

A. The associated hypoxia and hypercarbia may cause secondary brain injury. The high airway pressures required to maintain acceptable gas exchange may exacerbate intracranial hypertension.

Link to PACT module on Acute respiratory failure
Link to PACT module on Mechanical ventilation
A rapid sequence intubation is performed, according to the PACT module on Airway management. Numerous food particles are found in the visible airway and on respiratory suctioning. Mechanical ventilation and oxygenation present no problems, however.

Q. How do you proceed to establish the diagnosis of the coma?
A. A reassessment with a thorough clinical examination is needed, recognising that it is more difficult to assess a sedated and paralyzed patient.

While examining the patient you find a bleeding occipital laceration.

Q. What diagnostic procedures should you now consider?
A. A computed tomography (CT) scan is now the most appropriate diagnostic procedure because of the associated anisocoria and deep coma, which suggests intracranial hypertension.

Q. The history of the heavy fall and the finding of the laceration also suggest a traumatic injury. Is there a drug therapy that can be considered now for suspected acute intracranial hypertension?
A. Mannitol can be considered at this stage.

See PACT on Traumatic brain injury

Radiological studies in the patient with altered consciousness
PACT module on Patient transportation

A CT scan reveals a large right-sided parieto-occipital subdural haematoma, minor subarachnoid haemorrhage and an occipital fracture, without signs of brain swelling. You consult the neurosurgical team and the patient is immediately transferred to the operating theatre, where the haematoma is evacuated. Intracerebral pressure monitoring is initiated. Perioperatively, the anaesthetist has increasing problems with mechanical ventilation and oxygenation. Postoperatively, the patient is brought to the ICU.

Q. What are the possible reasons for these respiratory problems?
A. Possible explanations include acute lung injury as a result of the aspiration, or neurogenic pulmonary oedema.

Q. What diagnostic procedures do you perform?
A. You perform a chest X-ray to rule out atelectasis and seek evidence of (non-cardiogenic) pulmonary oedema.

PACT module on Clinical imaging – the Chest X-ray
Q. The chest X-ray confirms the presence of multiple bilateral interstitial and air-space pulmonary infiltrates. How do you ventilate this patient?

A. You should ventilate the patient using a lung-protective strategy but avoid hypercarbia.

Link to PACT module on Acute respiratory failure


The patient arrives in the ICU, already orotracheally intubated and sedated. In the first few hours in the ICU, the patient develops oliguria and signs of acute renal failure.

Link to PACT module on Oliguria and anuria (Acute Kidney Injury Part I)

Sedation is achieved with propofol infusion and intermittent i.v. boluses of fentanyl. Twenty-four hours later you consult the neurosurgeon and agree that sedation can be stopped. The patient becomes very agitated, but moves all his extremities, and has no focal neurological signs. Clinically, the patient is delirious.

Differential diagnosis of delirium


Q. Which conditions should be considered in the differential diagnosis of delirium and which would you consider as the most likely in this patient?

A. Delirium can be a reaction to a variety of metabolic, anoxic, toxic, and infective insults. The most likely cause of delirium in this patient is alcohol withdrawal syndrome.

Q. How do you treat alcohol withdrawal syndrome pharmacologically?

A. Benzodiazepines are the first-line treatment; another option would be clonidine. Haloperidol should be avoided because it can aggravate the delirium tremens and lower the seizure threshold.

Q. Which other general supportive measures would be appropriate.

A. Give vitamin B-complex, nutrition (enterally if possible) and electrolytes – especially magnesium and pay attention to fluid therapy and balance.
The patient is again sedated, now with a midazolam infusion, targeted to a Ramsay score of 5–6 according to a sedation protocol. Interruption of sedation, normally performed on a daily basis, is not performed in this case, and the patient remains oligo-anuric over the following three days. The creatinine level rises to 400 micromol/L (4.5 mg/dL) and the urea level to 37 mmol/L (2.3 mg/dL). When the sedative drug is discontinued in order to evaluate the neurological status, the patient does not wake up. A neurological exam shows no signs of intracranial hypertension, normal musculoskeletal reflexes, and pupillary reaction.

**Daily interruption of sedation and sedation protocols help to avoid overly deep sedation.**


**Link to PACT module on Sedation and analgesia**

**Q. Make a differential diagnosis for this new coma**

A. Intracranial pathology; infective complication; metabolic encephalopathy; prolonged action of sedative agents in presence of renal failure.

**Q. Describe your diagnostic steps**

A. You should perform a complete physical and laboratory examination, a CT to exclude intracranial pathology, and lumbar puncture to exclude postoperative infective complications. Look for evidence of sepsis other than cerebral origin.

**Causes of coma**

**Link to PACT module on Sedation and analgesia**

During your work-up, you find a nosocomial pneumonia with new left basal infiltrate on the chest X-ray, purulent sputum, and laboratory signs of infection including elevated leukocytes with 35% immature leukocytes. The CT scan is unremarkable except for minimal cerebral oedema. CSF studies were normal.

**Q. Taking into account the clinical course and the results of your investigations what is your analysis of the aetiological factors contributing to this likely multifactorial episode of coma?**

A. Septic encephalopathy (nosocomial pneumonia) and metabolic encephalopathy (renal failure with elevated urea) and accumulation of sedative agents.
Q. How likely is seizure activity? Is an immediate electroencephalogram (EEG) required to rule out non-convulsant epilepsy?

A. As there are other apparent causes for the coma/encephalopathy, it would be reasonable to treat these factors first and then review.

**Note** Secondary comatose states are often multifactorial.

You start antibiotic therapy for nosocomial pneumonia and begin renal replacement therapy. A pharmacological reversal of possible renal failure-associated, sedative metabolites (OH-midazolam-glucuronide) is contraindicated because of the previous seizure. After a few days, the patient gradually awakens and is found to be cooperative without any neurologic deficit.

Link to PACT module on Acute renal failure (Acute Kidney Injury Part II)

**On reflection**, the physical, psychological and socio-economic burden of unfavourable clinical outcomes following cerebral insults is tremendous. Secondary brain injuries are avoidable or treatable by appropriate management, and can usually be prevented. Basic and advanced knowledge of, and skills related to, the management of these patients are important for good clinical outcomes.