Coma, CNS Neoplasia and other neuro-muscular abnormalities in ITU: Part b

Author: S. Skellett, Aug 2005
Updated: T. Jerrom & M. Cooper, March 2016

1. Prior knowledge

Coma:
- Definitions & diagnosis of altered mental state, coma, PVS
- Drug overdose and poisoning
- Basics of status epilepticus
- Trauma

Other neurological conditions requiring ITU support.
- Spinal muscular atrophy
- Poliomyelitis
- Tetanus
- Posterior fossa tumours (medulloblastoma, astrocytoma): Symptoms, signs, diagnosis, emergency treatment, role of steroids, definitive treatment, outcome
- Hemispheric, third ventricle, metastatic tumours and craniopharyngiomas

Information for Year 1 ITU Training (basic):

Specific CNS conditions frequently seen on PICU:

The range of different neurological conditions seen on PICU is vast and for this reason this module has been split into two parts:
- Coma, CNS Neoplasia and other neuro-muscular abnormalities in ITU: Part a
- Coma, CNS Neoplasia and other neuro-muscular abnormalities in ITU: Part b

The following conditions and their management on PICU will be discussed in this module. Each is a large topic in their own right and the following notes are simply meant to be a brief introduction to the topics highlighting some of the important issues:
- Brain stem death and brain stem death testing
- Injuries to the peripheral nervous system
  - Brachial plexus injuries
Brain stem death and brain stem death testing:

The Academy of Medical Royal Colleges (2008) “A Code of Practice for the Diagnosis and Confirmation of Death” describes how;

“Death entails the irreversible loss of those essential characteristics which are necessary to the existence of a living human person and, thus, the definition of death should be regarded as the irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe. The irreversible cessation of brain-stem function whether induced by intra-cranial events or the result of extra-cranial phenomena, such as hypoxia, will produce this clinical state and therefore irreversible cessation of the integrative function of the brain-stem equates with the death of the individual and allows the medical practitioner to diagnose death.”

Brain death in children most commonly occurs as a result of trauma and anoxic encephalopathy. The Academy of Medical Royal Colleges (AoMRC) Code of Practice for the Diagnosis and Confirmation of Death set down specific criteria and codes of conduct around how Brain Stem Death (BSD) should be diagnosed.

**The Academy of Medical Royal Colleges (2008) “A Code of Practice for the Diagnosis and Confirmation of Death” can be accessed at:**
- http://www.aomrc.org.uk

Their guideline has been condensed by the Faculty of Intensive Care Medicine (FICM) and a section of this is included below:

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<table>
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<tr>
<th>Exclusion of Reversible Causes of Coma and Apnoea</th>
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<td>1st Test Dr One</td>
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<tr>
<td><strong>Is the coma due to depressant drugs? Drug Levels (if taken):</strong></td>
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<td><strong>Is the patient’s body temperature ≤34°C?</strong></td>
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<td><strong>Is the apnoea due to neuromuscular blocking agents, other drugs or a non brain-stem cause (eg. cervical injury, any neuromuscular weakness)?</strong></td>
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A summary of the FICM abbreviation of the Code of Practice for the Diagnosis and Confirmation of Death can be found in Appendix 1.

This guidance however excluded infants below 2 months of age (due to a lack of evidence surrounding the presence of the required criteria in 2008) making BSD testing and subsequent beating heart organ donation impossible in neonates and young babies. To address this issue RCPCH updated its 1991 guidance on the ‘Diagnosis of Brain Stem Death in Infants and Children: A Working Party report by the British Paediatric Association’ to produce recommendations on the diagnosis of death by neurological criteria (DNC) in infants from 37 weeks corrected gestation (post menstrual) to two months post term. For infants older than two months the 2008 AoMRC ‘A Code of Practice for the Diagnosis and Confirmation of Death’ recommendations continue to apply.

The RCPCH published its guideline on The diagnosis of death by neurological criteria in infants less than two months old April in 2015:

A summary of the RCPCH guideline on The diagnosis of death by neurological criteria in infants less than two months old can be found in Appendix 2.
Injuries to the peripheral nervous system:

There are a number of peripheral nerve injuries that are seen on PICU, the most common of which are:

- Brachial plexus injuries
- Nerve injuries sustained on PICU
- Trauma to the peripheral nervous system

Brachial plexus injuries

Brachial plexus injuries can occur as a result of shoulder trauma, tumors, or inflammation. In infants, brachial plexus injuries most commonly occur secondary to shoulder dystocia. Two main clinical pictures are seen depending on the site of the nerve injury:

- **Erb-Duchenne (Erb’s) palsy** refers to paralysis of the upper brachial plexus (C5 and C6 roots).
  - The signs of Erb's Palsy include loss of sensation in the arm and paralysis and atrophy of the deltoid, biceps, and brachialis muscles. The arm hangs by the side and is rotated medially; the forearm is extended and pronated. The arm cannot be raised from the side; all power of flexion of the elbow is lost, as is also supination of the forearm. The resulting biceps damage is the main cause of this classic physical position commonly called "waiter's tip."

- **Dejerine-Klumpke (Klumpke's) palsy** refers to paralysis of the lower brachial plexus (C8 and T1 roots).
  - Symptoms include intrinsic minus hand deformity, paralysis of intrinsic hand muscles, and C8/T1 Dermatome distribution numbness. Involvement of T1 may result in Horner's syndrome, with ptosis, and

The following articles and websites also provide excellent information on the topic of brain stem death, organ donation and end of life care:

- NICE (2011) “Organ Donation for Transplantation”
  [http://guidance.nice.org.uk/CG135](http://guidance.nice.org.uk/CG135)
  [http://bja.oxfordjournals.org/content/108/suppl_1/i14.full](http://bja.oxfordjournals.org/content/108/suppl_1/i14.full)
- Together for short lives
  [http://www.togetherforshortlives.org.uk/professionals/resources](http://www.togetherforshortlives.org.uk/professionals/resources)

The following UpToDate article provides a good synopsis of brain stem death:


**UpToDate can be accessed via the Athens portal using your OpenAthens login.**
miosis. Weakness or lack of ability to use specific muscles of the shoulder or arm

There are four types of brachial plexus injuries:

- **Avulsion**, the most severe type, in which the nerve is torn from the spine.
- **Rupture**, in which the nerve is torn but not at the spinal attachment.
- **Neuroma**, in which the nerve has torn and healed but scar tissue puts pressure on the injured nerve and prevents it from conducting signals to the muscles.
- **Neuropraxia** or stretch, in which the nerve has been damaged but not torn. Neuropraxia is the most common type of brachial plexus injury.

Many children who are injured during birth improve or recover by 3 to 4 months of age. Treatment for brachial plexus injuries includes physiotherapy however some children need surgery.

There is a rare syndrome called Parsonage-Turner Syndrome, or brachial plexitis, which causes inflammation of the brachial plexus without any obvious shoulder injury. This syndrome can begin with severe shoulder or arm pain followed by weakness and numbness.

**Nerve injuries sustained on PICU**

Perioperative peripheral nerve injuries are a common and potentially catastrophic complication of anaesthesia and are also seen on PICU. These injuries can cause a range of morbidity from transient and clinically minor injury, through to severe permanent injury.

The following journal article provides an excellent synopsis of peripheral nerve injuries associated with anaesthesia:


Peripheral nerve injuries are often related to positioning of the patient causing direct compression to the nerve. This is not always the case however for the ulnar nerve in which spontaneous injury can occur where there is not obvious mechanism of injury. Pressure applied over nerves can damage neurons, cause ischaemic insult, and lead to necrosis. These pressure injuries are most likely when nerves are anatomically exposed to external compression. Avoiding hypotension and treating coagulopathy are also important in preventing peripheral neuronal injury.

Good patient positioning on a pressure relieving mattress, the use of gel pad for exposed areas and regular repositioning are vital in preventing these types of injuries. The head and neck must be in a neutral position to help avoid vascular or neural injury. Shoulder abduction with lateral rotation should be avoided where possible to avoid brachial plexus stretch. Upper limb joints should not extend beyond ninety degrees. Forearm supination helps protect the ulnar nerve, as prolonged pronation of the forearm can compress the ulnar nerve in the cubital tunnel.
Trauma to the peripheral nervous system

Nerve injury due to trauma occurs from traction/stretch, laceration, compression, or ischemia to the nerve. The nerve injury is often initially due to the direct mechanical forces applied to the nerve fibres which then often suffer a secondary injury due to vascular compromise leading to ischemic nerve damage.

Common locations of nerve injuries caused by trauma include the following:
- Median neuropathies most commonly occur at the wrist.
- Ulnar syndromes occur most often at the elbow and the wrist.
- Radial neuropathies commonly develop in the mid-upper arm.
- Sciatic neuropathies occur most often in the gluteal region.
- Peroneal neuropathies most frequently occur at the fibular head.
- Tibial neuropathies most often occur at the tarsal tunnel.

The diagnosis of traumatic mononeuropathy is primarily clinical and is based upon the presence of neurologic symptoms and signs of a mononeuropathy with a consistent history. Electrodiagnostic testing provides information regarding localization, severity, and prognosis of the nerve injury. Ultrasound is also being increasingly used to aid diagnosis.

Treatment of traumatic neuropathy is either conservative with close follow-up or surgical when appropriate and differs according to whether the injury is open or closed. Early involvement of the plastic and or orthopaedic surgical team is vital.
## Post Year 1 Module Quiz:

### Regarding brain stem death testing:

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The following conditions and their management on PICU will be discussed in this module. Each is a large topic in their own right and the following notes are simply meant to be a brief introduction to the topics highlighting some of the important issues:

- Guillian Barré syndrome
- Myasthenia Gravis
- Metabolic and genetic abnormalities that can cause encephalopathy
- Acute disseminated encephalomyelitis (ADEM)
- Status epilepticus
- Neuromuscular weakness related to critical illness
- Hypotonia, neuropathies and myopathies
- Dystonia and status dystonicus

Guillain-Barré syndrome:

The Guillain-Barré syndromes (GBS) are acute immune-mediated polyneuropathies. Historically, GBS was considered a single disorder but it is now known to be a heterogeneous collection syndrome with several different variants. GBS most commonly presents as an acute monophasic paralyzing illness triggered by a preceding infection. In addition to the demyelinating form (which is most common) there are also axonal forms, which often have a poorer prognosis.

The following UpToDate article provides an excellent synopsis of the epidemiology, clinical features, and diagnosis of Guillain-Barré syndrome in children:


UpToDate can be accessed via the Athens portal using your OpenAthens login.

Lawn et al (2001) showed that progression to mechanical ventilation in adults with GBS was highly likely if they had:

- Bilateral facial weakness
- Severe rapidly progressive course.
- Bulbar palsy with symptoms.
- Autonomic cardiovascular instability; i.e. persistent hypertension or labile blood pressure, or arrhythmias
Lawn et al (2001) also showed that the following factors are associated with progression to respiratory failure in adults:

- Vital capacity of less than 20 mL/kg.
- Maximal inspiratory pressure less than 30 cm H₂O.
- Maximal expiratory pressure less than 40 cm H₂O.
- A reduction of more than 30% in vital capacity, maximal inspiratory pressure, or maximal expiratory pressure.

In their study no clinical features predicted the pattern of respiratory decline; however, serial measurements of pulmonary function tests allowed detection of those at risk for respiratory failure. They concluded that while inherently unpredictable, the course of patients with severe GBS can, to some extent, be predicted on the basis of clinical information and simple bedside tests of respiratory function. This data may be used in the decisions regarding admission to the intensive care unit and preparation for elective intubation.

The main modalities of therapy for Guillain-Barré syndrome include plasmapheresis and administration of intravenous immune globulin.

- Both intravenous immunoglobulin (IVIG) and plasmaphoresis (plasma exchange) have been proven to accelerate the rate of recovery in Guillain-Barre Syndrome.
- There is no significant difference in therapeutic efficacy between plasma exchange and intravenous immunoglobulin. There are clear practical advantages to using immunoglobulins. A combination of both treatments shows only a trend favouring that approach.
- 10% of early treated patients will relapse in the following 10 days.
- Retreatment is recommended in cases of relapse (using half of the original dose of immunoglobulin).
- Late treatment (treatment instituted more than three weeks after the first symptoms) is not of any proven benefit.

Intravenous immunoglobulin (IVIG) should be given in the following circumstances:

- Patient is deteriorating at the time the diagnosis is made, irrespective of the functional state of the child or physical findings.
- Patient is non-ambulant at the time of diagnosis.
- Any evidence of bulbar or respiratory dysfunction at diagnosis.

Suggested schedule for IVIG:

- Total dose of 2g/kg, divided into 5 consecutive daily doses of 400mg/kg each or 3 consecutive days of 700mg/kg each.
- Or a 2g/kg continuous infusion over 3 days.
- Or a single dose (2g/Kg) infusion over 24 hours

Plasmaphoresis improves the clinical course of acute GBS as measured by time to recovery of muscle strength and independent ambulation and by outcome at 6 months. Best if instituted within 7 days of the onset of disease and in those who subsequently required mechanical ventilation.

Currently however due to the more invasive nature of this therapy, there is no indication for using plasmaphoresis in preference to immunoglobulins.
Plasmaphoresis schedule as follows:
- 50ml/kg over 7 days (using plasma exchange on the 1st, 3rd, 5th & 7th day)
- Two exchanges will benefit mild cases, four exchanges are preferable for moderate or severe cases

Advantages of Plasmaphoresis:
- Unequivocally proven accelerated rate of recovery.
- Anecdotally, potentially useful in cases of relapse post IVIG.

Disadvantages of Plasmaphoresis:
- Difficulty with venous access, placement and maintenance; infection.
- Cardiovascular symptoms, mainly hypotension.
- Difficulty in completing treatment course (10-15% failed to complete course vs 5% for IVIG).

Corticosteroids should not be used in the treatment of GBS however if a patient requires steroids for some other reason its use will probably do no harm.

Pain is present in 50-80% of patients with GBS at the time of presentation:
- Pain is common during the recovery phase of muscle weakness. Between 70 and 90% have persistent pain or new pain over the first month or two of the illness
- Pain in GBS is commonly due to:
  o Inflammation and entrapment of the nerve roots (back and limbs).
  o Alteration in the function or spontaneous discharges in the demyelinated sensory nerves (i.e. paraesthesia, causalgia).
- Children may need opioids to keep pain free. Non steroidal are useful in acute non-severe pain.
- Carbamazepine is effective as an adjuvant treatment for neuralgic pain during the recovery phase in PICU.
- Tricyclics and pregabalin are also effective in neuralgic pain.

Other important issues in the management of patients with GBS (and other conditions causing significant immobility) in PICU include:
- Air mattresses.
- Turning patients and careful positioning of limbs.
- Padding of elbows and knees.
- Appropriate splinting (ankles, wrists).
- Continuation of enteral feeding, effective antacids, e.g. omeprazole
- The child may be fully aware and conscious of the surroundings, despite paralysis. Everything that is said in front of the child is likely to be heard.
- It is important that the child is told what is happening and should be reassured by familiar voices and faces.
- A calm atmosphere is essential.
- The environment should be as child-friendly as possible. Bring in a favourite toy.
- Speech and language therapists and occupational therapists should be involved early. They will be able to assess the patients’ need for augmented and alternative communication devices.
- Anti-thrombotic prophylaxis:
Anti-thrombotic stockings should be used in all children >10 years, until lower limbs can move freely.

Consider using low dose heparin in children >12 years.

Myasthenia Gravis:

Myasthenia gravis (MG) is an autoimmune disease in which antibodies target the postsynaptic membrane of the neuromuscular junction, leading to muscle severe weakness and fatigability. Prepubertal children with the condition have a higher prevalence of isolated ocular symptoms, lower frequency of acetylcholine receptor antibodies but fortunately a higher probability of achieving remission. Juvenile MG is primarily a clinical diagnosis with classical patterns of fluctuating weakness and fatigability. Diagnosis in young children can be complicated by the need to differentiate from congenital myasthenic syndromes, which do not have an autoimmune basis (Finnis & Jayawant, 2011).

Investigations for MG often include:

- Serology: Detection of antibodies to the AChR supports the diagnosis of JMG
- Tensilon test: This involves intravenous infusion of edrophonium, a fast-acting, short-duration cholinesterase inhibitor. This prevents the breakdown of acetylcholine, thereby increasing the concentration of the neurotransmitter at the neuromuscular junction. The patient is observed, and ideally a video recorded, looking for a transient improvement in previously documented weakness, for example, ptosis, dysphonia. This test is not without risk and should only be performed by staff experienced in paediatric resuscitation, due to the cholinergic effects of edrophonium, which can result in bradycardia, nausea, and excess salivation.
- Electrophysiological testing can be invaluable in investigation of suspected Juvenile MG. Repetitive nerve stimulation in JMG will show a decrement in the compound motor action potential of >10% by the 4th or 5th stimulation.
- Imagining: Although thymoma in children is rare, the thymus must be imaged (usually by CT) once JMG has been diagnosed.

(Finnis & Jayawant, 2011)

Treatment commonly includes anticholinesterases, corticosteroids with or without steroid-sparing agents, and newer immune modulating agents. Plasma exchange and intravenous immunoglobulin (IVIG) are effective in preparation for surgery and in treatment of myasthenic crisis. Thymectomy increases remission rates.

The following UpToDate article provides an excellent synopsis of the treatment and prognosis of Guillain-Barré syndrome in children and also talks in more detail about PICU admission criteria:


UpToDate can be accessed via the Athens portal using your OpenAthens login.
There are potential anaesthetic concerns which need to be considered in patients with myasthenia gravis. These include the potential interactions between the patient’s existing drug treatments and the medications used for anaesthesia, particularly neuromuscular blocking agents (NMBAs). Patients with MG are unpredictably sensitive to nondepolarizing NMBAs and are resistant to succinylcholine.

The following UpToDate article provides a good synopsis of the anesthetic considerations needed for patients with myasthenia gravis:


UpToDate can be accessed via the Athens portal using your OpenAthens login.

There are a number of medications that can affect neuromuscular transmission. In normal patients, these effects are usually of no consequence, but in patients with MG, they can exacerbate muscle weakness, especially in the presence of residual anaesthetic agents.

Several classes of antibiotics can affect neuromuscular transmission, including aminoglycosides (eg, gentamicin) and polymyxins. There are case reports of ampicillin (but not other penicillin-based antibiotics), macrolides (eg, erythromycin, azithromycin), tetracycline, and fluoroquinolones (eg, ciprofloxacin) causing weakness.

Other medications with the potential to exacerbate weakness include certain local anaesthetics, beta blockers, calcium channel blockers, antiepileptics (Gabapentin and phenytoin), phenothiazines, diuretics, procainamide, magnesium, and opioids.

**Metabolic and genetic abnormalities that can cause encephalopathy:**

A large number of metabolic and genetic abnormalities may cause encephalopathy. Inborn errors of metabolism that present in the new-born period typically share strikingly similar clinical features, including decreased level of consciousness, seizures, poor feeding, hypotonia, and vomiting. Examples include:

- Disorders of amino acid metabolism (eg, maple syrup urine disease, phenylketonuria, nonketotic hyperglycinemia)
- Hyperammonemia (eg, urea cycle defects)
- Neonatal hypoglycaemia
- Organic acidemias
- Mitochondrial disorders
- Severe peroxisomal disorders (eg, Zellweger syndrome)

Specific disorders such as multiple sulfite oxidase deficiency may produce neuroimaging and clinical findings that very closely mimic hypoxic-ischemic brain injury. Genetic
disorders such as Prader-Willi and chromosomal abnormalities may also present with new-born encephalopathy.

The following is a list of the Laboratory Studies suggested by Burton (1998) for an infant suspected of having an inborn error of metabolism:

- Complete blood count with differential
- Urinalysis Blood gases
- Serum electrolytes
- Blood glucose
- Plasma ammonia
- Urine reducing substances
- Urine ketones if acidosis or hypoglycaemia present
- Plasma and urine amino acids, quantitative
- Urine organic acids
- Plasma lactate

The following paper although now quite old provides a very good summary of the most common inborn errors of metabolism in infancy and their investigation:


This paper has a number of investigations decision trees for different situations which are very useful, e.g.
If you suspect that a child may have a metabolic disorder that has decompensated then their care needs to be discussed with the local metabolic team. Each specific metabolic disorder requires a specific treatment.

The British Inherited Metabolic Disease Group (formed in 1989) has an excellent website with emergency treatment regimens for most metabolic conditions and also for the emergency management of as yet undiagnosed patients presenting in extremis.

The British Inherited Metabolic Disease Group website can be access via this link:


As well as guidelines on specific conditions it also has a range of different fluid calculators which are also very helpful, including:
- Hyperammonaemia: How to make up intravenous solutions
- Making intravenous fluids for metabolic patients
- UCD medicines - dose calculator

**Acute disseminated encephalomyelitis (ADEM):**

Acute disseminated encephalomyelitis (ADEM), also known as post infectious encephalomyelitis, is a demyelinating disease of the central nervous system. It classically presents as a monophasic disorder associated with multifocal neurologic symptoms.

The following UpToDate article provides an excellent synopsis of acute disseminated encephalomyelitis in children, its pathogenesis, clinical features, and diagnosis:


UpToDate can be accessed via the Athens portal using your OpenAthens login.

ADEM is fortunately an uncommon illness, Leake et al (2004) estimates incidence in California is 0.4/100,000 population per year. There is no specific ethnic distribution but there may be a slight male predominance.

ADEM is often preceded by a viral or bacterial infection, usually in the form of a nonspecific upper respiratory infection. <5% ADEM cases follow immunization.

The pathogenesis of ADEM is poorly understood however it appears to be an autoimmune disorder of the central nervous system that is triggered by an environmental stimulus in genetically susceptible individuals. The proposed mechanism is that myelin autoantigens, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein, share antigenic determinants with those of an infecting pathogen (Stonehouse et al, 2003). This causes a cell-mediated delayed hypersensitivity reaction which leads to the demyelination.
The immunopathological events leading to ADEM can be divided into two major phases (Becher et al, 2006):
- Initial T cell priming and activation
- Subsequent recruitment and effector phase

In ADEM neurologic symptoms typically appear 4-13 days after the trigger infection or vaccination. 50-75% of children with ADEM have had a febrile illness in the 4 weeks prior to the onset neurologic symptoms. Fever, headache, vomiting, and meningismus are commonly seen at the initial presentation. The characteristic feature of encephalopathy swiftly develops in association with multifocal neurologic deficits following these initial symptoms. Maximal deficits usually occur over 4-7 days (Tenembaum et al, 2007). Seizures occur in only 1/3 of patients.

In addition to encephalopathy, the most common neurologic features of ADEM include:
- Long tract (pyramidal) signs
- Cranial neuropathies (including optic neuritis)
- Acute hemiparesis
- Cerebellar ataxia
- Spinal cord dysfunction (transverse myelitis, which can cause respiratory failure).

The clinically most severe phase of ADEM typically lasts 2-4 weeks. Children usually recover completely from the acute illness, although some have neurologic sequelae.

The diagnosis of ADEM is based upon the clinical and radiologic features as there is no specific biologic marker or other confirmatory test (Tenembaum et al, 2007). Other differential diagnoses however need to be excluded with further testing.

Diagnostic criteria for ADEM in children below have been proposed by the International Pediatric Multiple Sclerosis Study Group (Krupp et al, 2013).

### Diagnostic criteria of acute disseminated encephalomyelitis (ADEM) in children

**Clinical Features (all are required):**
- A first polyfocal, clinical central nervous system event with presumed inflammatory demyelinating cause.
- Encephalopathy that cannot be explained by fever, systemic illness, or postictal symptoms.
- No new clinical and MRI findings emerge three months or more after the onset.
- Brain MRI is abnormal during the acute (three-month) phase.

**Lesion characteristic on MRI Brain:**
- Diffuse, poorly demarcated, large (>1 to 2 cm) lesions involving predominantly the cerebral white matter.
- Deep grey matter lesions (eg, involving the basal ganglia or thalamus) can be present.
- T1 hypointense lesions in the white matter are rare.

The International Paediatric Multiple Sclerosis Study Group (Krupp et al, 2013) also describe two patterns of ADEM:
• **Monophasic ADEM**: The clinical features of ADEM typically follow a monophasic disease course, although they can fluctuate in severity and evolve in the first three months following disease onset.

• **Multiphasic ADEM**:Defined as two episodes consistent with ADEM separated by three months, irrespective of steroid use, but not followed by any further events.

There are also a number of hyperacute variants of ADEM which can cause inflammatory haemorrhagic demyelination of central nervous system white matter. These include:

- Acute haemorrhagic leukoencephalitis (AHL)
- Acute haemorrhagic encephalomyelitis (AHEM)
- Acute necrotizing haemorrhagic leukoencephalitis (ANHLE) of Weston Hurst

The mainstay of treatment for ADEM is high-dose intravenous glucocorticoids (Alper, 2012).

- There are many different treatment regimens. One is Methylprednisolone (30 mg/kg per day, up to a maximum dose of 1000 mg per day) for five days, followed by a four to six week oral prednisone taper for those with residual symptoms after intravenous treatment.

Additional treatments include intravenous immune globulin and plasma exchange (Tenembaum et al, 2007) for those with longitudinally extensive transverse myelitis and who have failed to respond to steroids. However, the effectiveness of these treatments has not been definitively confirmed as there are no prospective clinical trial data to determine optimal treatment, including dose or duration. There is however sufficient clinical experience and small trials supporting their use.

All children should receive long-term neurological follow-up to document recovery and to confirm the diagnosis of ADEM. The occurrence of relapses suggests alternative diagnoses, such as multiphasic ADEM or multiple sclerosis.

Most children with ADEM make a full recovery, usually slowly over four to six weeks. At follow-up, approximately 60-90% have minimal or no neurologic deficits.

The prognosis for survival and recovery of neurologic function is worse for the hyperacute haemorrhagic variants of ADEM than for typical ADEM.

The following UpToDate article provides an excellent synopsis of acute disseminated encephalomyelitis in children, its treatments and prognosis:


UpToDate can be accessed via the Athens portal using your OpenAthens login.

**Status epilepticus:**

Status epilepticus (SE) is the most common medical neurologic emergency in childhood. The duration of continuous seizure activity used to define status epilepticus (SE) has been recently modified by the International League Against Epilepsy (Trinka et al 2015).
SE is now defined by the ILAE as:

- A condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures, after time point t1.
  - Time point t1 = 5 minutes for generalized convulsive SE.
  - Time point t1 = 10 minutes for focal SE with impaired consciousness.
  - Time point t1 = 10 minutes for absence SE.
- A condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures
  - Time point t2 = 30 minutes for generalized convulsive SE.
  - Time point t2 = >60 minutes for focal SE with impaired consciousness.
  - Time point t2 = 15 minutes for absence SE.

Shinnar et al (2001) found that a convulsive seizure lasting more than five minutes has a high risk of lasting >30 minutes and Eriksson et al (2005) found that treatment delay is associated with delayed seizure termination.

The types of EEG patterns that should be considered ictal in patients without clinical manifestations (subclinical seizures) are controversial. Some argue that periodic epileptiform activity (commonly seen in severe hypoxic-ischemic encephalopathy) are definite seizures requiring treatment (Abend & Dlugos 2007) whereas other experts consider this activity to be interictal and would not treat it in isolation (Nei et al, 1999).

<table>
<thead>
<tr>
<th>The management of seizures on PICU, (including; aetiology, diagnosis, monitoring and treatment) is a vast but very important topic.</th>
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<td>The following article provides an excellent synopsis of the management of seizures on PICU:</td>
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</table>

The critically ill mechanically ventilated child with ongoing seizures that are refractory to any treatment presents a distinct challenge in pediatric neurocritical care. The evidence base from randomized controlled trials on which anti-epileptic drug (AED) strategy should be used is inadequate. This review of refractory and super-refractory status epilepticus summarizes recent pediatric case series regarding definitions, the second-tier AED therapies once initial anticonvulsants have failed, and the experience of high-dose midazolam, barbiturate anesthesia, and volatile anesthetics for uncontrolled status epilepticus.

It can be accessed by following the attachment below:
- [https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S074907041200108X?locale=en_US](https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S074907041200108X?locale=en_US)

The International League Against Epilepsy (ILAE)
The ILAE was founded in 1909 and is an organisation of more than 100 national chapters. The goals of the ILAE are:
- To advance and disseminate knowledge about epilepsy
- To promote research, education and training
- To improve services and care for patients, especially by prevention, diagnosis and treatment

The ILAE website can be accessed by following this attachment (http://www.ilae.org). It is an excellent source of information on all aspects of seizures and has specific paediatric guidelines on the following topics:

- **Summary of recommendations for the management of infantile seizures**: Task Force Report for the ILAE Commission of Pediatrics (2015)
- **ILAE Guidelines for imaging infants and children with recent-onset epilepsy** (2009)
- **Guidelines on Neonatal Seizures** (WHO, ILAE) (2011)
- **Pregnancy registries: Differences, similarities, and possible harmonization**, 2010
- **Infantile spasms: A U.S. consensus report**, 2010
- **Management issues for women with epilepsy** – Focus on pregnancy, an evidence-based review:
  - Obstetrical complications and change in seizure frequency, (2009)
  - Teratogenesis and perinatal outcomes (2009)
  - Vitamin K, folic acid, blood levels, and breast-feeding (2009)

The following UpToDate article provides a good synopsis of status epilepticus in children:

The following UpToDate article provides a good synopsis of the management of convulsive status epilepticus in children:

UpToDate can be accessed via the Athens portal using your OpenAthens login.

**Neuromuscular weakness related to critical illness:**

Neuromuscular weakness is a common complication of critical illness in children and adults. In adult studies ≥25% of patients who are in the intensive care unit (ICU) and ventilated for at least seven days develop some sort of neuromuscular weakness related to critical illness (De Jonghe *et al*, 2002)

Critical illness associated weakness is partly a consequence of improved survival in patients with multiorgan failure and sepsis, but is also a side effect of medications used on PICU (particularly glucocorticoids and paralytic agents).
Neuromuscular weakness in the ICU is most often due to critical illness myopathy (CIM) or critical illness polyneuropathy (CIP).

In CIM there is preservation of sensory function distinguishing it from CIP. However, sensory evaluation can be difficult in critically ill patients, particularly when the child is obtunded, comatose, or intubated, and it may be difficult to distinguish CIM from CIP on the basis of clinical features and neurologic examination findings alone. Some patients can have features of combined CIM and CIP and both conditions lead to delayed extubation and increased morbidity and mortality.

Other differentials of critical illness associated weakness include:
- Rhabdomyolysis
- Cachectic myopathy;
  - A subacute myopathy due to protein catabolism and disuse and a diagnosis of exclusion. There is proximal-predominant weakness with muscle wasting, a normal serum creatine kinase (CK), laboratory evidence of malnutrition, normal or mildly ‘myopathic’ motor unit potential changes on EMG without fibrillation potentials, and type 2 muscle fibre atrophy histologically.
- Guillain-Barré syndrome
- Prolonged neuromuscular junction blockade (rare);
  - This disorder is related to prolonged use (days) of paralytic agents, often in the setting of renal or hepatic insufficiency, leading to prolonged circulation of drug metabolites.

**Critical illness myopathy (CIM)**

Critical illness myopathy (also known acute quadriplegic myopathy and thick filament myopathy) is the commonest form of ICU acquired myopathy (Koch et al, 2011. Latronico & Bolton, 2011)


IV steroids are used in the treatment of each of these conditions and their use is the strongest risk factor for CIM. There is also some correlation between the likelihood of occurrence and severity of disease with glucocorticoid dose (Amaya-Villar et al, 2005. Douglass et al, 1992). However, there are rare cases where patients have not received any steroids. Another potential risk factor for CIM is the use of various types of paralytic agents.
CIM usually begins several days after IV steroids are started. The most common presenting features of CIM are (Campellone et al, 1998):

- Flaccid quadripareisis that may affect proximal more than distal muscles.
- Delay or inability to wean off mechanical ventilation.

Facial muscle weakness is also relatively common whereas extraocular muscle weakness rarely occurs. In CIM sensation should be normal however on PICU it is often difficult to assess due to various factors. Deep tendon reflexes may be normal or reduced.

The major histopathologic finding in CIM is relatively selective loss of myosin (lack of reactivity to myosin ATPase in non-necrotic fibers). Immunohistochemical studies for myosin or electron microscopy to identify loss of thick filaments can be used to confirm the histology.

The diagnosis of CIM is suspected in PICU patients who have the described clinical features particularly if they have been given steroids. An elevated serum creatine kinase (CK) is usually present but it can be raised in patients receiving IV steroids who do not have CIM (Douglass et al, 1992.)

The major diagnostic features of CIM are:

- Sensory nerve amplitudes >80 percent of the lower limit of normal in two or more nerves on NCS.
- Muscle histopathologic findings of myopathy with myosin loss.
- Needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials.
- Absence of a decremental response on repetitive nerve stimulation.

Supportive diagnostic features of CIM are:

- Motor amplitudes <80 percent of the lower limit of normal in two or more nerves without conduction block on nerve conduction studies (NCS).
- Muscle inexcitability on direct muscle stimulation.
- Elevated serum CK (best assessed in the first week of illness).

In adults CIM normally resolves over weeks to months (Latronico et al, 2005), but leads to significantly prolonged ICU and hospital stay. The goal is trying to avoid your patient developing CIM in the first place.

Once established, treatments for CIM include: (Lacomis, 2003. Mehrholz et al, 2015)

- Discontinuation or reduction of glucocorticoids as soon as possible.
- Aggressive management of medical conditions.
- Avoidance of additional complications such as venous thrombosis.
- Intensive rehabilitation

There is a weak evidence base that intensive insulin therapy (target blood glucose 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) may lower the incidence of CIM and CIP among critically ill patients who remain in the intensive care unit for seven or more days (Van den Berghe et al, 2005. Hermans et al, 2007. Hermans et al, 2014). These studies are limited by methodologic issues but it may prove to be an area of future interest.
Critical illness polyneuropathy (CIP)

Critical illness polyneuropathy was first recognized clinically in the late 1970s and is the second most common neuromuscular condition acquired in intensive care (Latronico & Bolton, 2011). CIP appears to be a common complication of severe sepsis in adults and is thought to represent a neurologic manifestation of the systemic inflammatory response syndrome (SIRS) (Latronico et al, 2005).

The mechanism of axonal injury in CIP is unknown, however there are theories relating to sepsis causing injury to the microcirculation of distal nerves leading to ischemia and axonal degeneration (Latronico et al, 2005).

In adults CIP usually occurs in patients who are in the ICU for ≥1 week and the clinical features can overlap with CIM. Patients with CIP demonstrate a sensorimotor polyneuropathy characterized by (Latronico et al, 2005):

- Limb muscle weakness and atrophy
- Reduced or absent deep tendon reflexes
- Loss of peripheral sensation to light touch and pin prick
- Relative preservation of cranial nerve function

As with CIM, it is often difficult to distinguish CIP from CIM or from combined CIM and CIP on the basis of clinical features and neurologic examination findings alone. The following diagnostic criteria for CIP are well established (Bolton, 2005):

- Setting of critical illness, particularly if complicated by sepsis, multiorgan failure, and the systemic inflammatory response syndrome.
- Difficulty weaning from ventilator that is not related to cardiopulmonary causes.
- Electrophysiologic evidence of axonal motor and sensory polyneuropathy.
- Possible limb weakness.

Although there is no consensus on specific electrodiagnostic and laboratory criteria for CIP, the following features support the diagnosis:

- Sensory and motor nerve amplitudes <80 percent of the lower limit of normal in two or more nerves on nerve conduction studies.
- Absence of conduction block or prolongation of F-waves.
- Absence of a decremental response on repetitive nerve stimulation.
- Needle EMG with reduced recruitment of normal motor unit potentials (MUPs) (early) followed by fibrillation potentials and reduced recruitment of long-duration, high-amplitude MUPs (after weeks).

In survivors of CIP with mild or moderate nerve injury, recovery of muscle strength normally occurs over weeks to months. However, electrodiagnostic testing may demonstrate residual nerve dysfunction several years after initial presentation and some patients with severe CIP remain quadriplegic.

As with CIM, treatment of CIP is supportive and includes aggressive management of sepsis and underlying medical conditions, avoidance of additional complications such as venous thrombosis, and rehabilitation (Mehrholz et al, 2015).
**Combined Critical Illness Myopathy and Polyneuropathy:**
Some PICU patients can develop a combination of both critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) (Latronico & Bolton, 2011). This combined disorder has also been termed critical illness polyneuromyopathy (CIM/CIP). Adults with CIM tend to have better outcomes than those with CIP. Electrodiagnostic studies with direct muscle stimulation show that patients with both CIM and CIP usually develop CIM first (Koch et al, 2011). Patients with CIM and CIP remain hospitalized longer than those with CIM alone.

**Mehrholz’s et al (2015) Cochrane review on the Physical rehabilitation for critical illness myopathy and neuropathy, clearly shows that CIP and CIM are important areas for future research.**
- Available at: file:///C:/Users/owner/Downloads/Mehrholz_et_al-2015-The_Cochrane_library.sup-1.pdf

"**Main results:** The search strategy retrieved 3587 references. After examination of titles and abstracts, we retrieved the full text of 24 potentially relevant studies. None of these studies met the inclusion criteria of our review. No data were suitable to be included in a meta-analysis."

"**Authors’ conclusions:** There are no published RCTs or quasi-RCTs that examine whether physical rehabilitation interventions improve activities of daily living for people with CIP and CIM. Large RCTs, which are feasible, need to be conducted to explore the role of physical rehabilitation interventions for people with CIP and CIM."

**Hypotonia, neuropathies and myopathies:**

Neuromuscular diseases frequently present in new-borns or infants with hypotonia and weakness. Infants can suffer from weakness and hypotona for a variety of reasons, including:
- Neuromuscular diseases (NMD)
- Central nervous system (CNS) disorders
- Sepsis
- Organ failure
- Metabolic dysfunction
- Drugs and toxins

Infants with NMD often have a history of polyhydramnios, foetal akinesia, and malpresentation. A family history of neuromuscular abnormalities may be present and needs to be sought out.

Physical findings that can aid diagnosis include:
- Dysmorphic features
- Bruising or petechiae
- Respiratory abnormalities
- Cardiomyopathy
• Organomegaly
• Abnormal genitalia (including hypogonadism)
• Joint contractures or laxity

Hypotonic infants will adopt a ‘frog-like’ position when supine, with decreased spontaneous movement and reduced muscle stretch resistance. In most CNS disorders tone is reduced to a greater extent than muscle strength, and infants retain antigravity power in their limbs. In NMD infants will often have reduced or absent antigravity movements.

This is a list of the most common cause of NMD presenting in new-borns:

Anterior horn cell disorders
• Acute infantile spinal muscular atrophy
• Traumatic myelopathy
• Hypoxic-ischemic myelopathy
• Arthrogryposis multiplex congenita

Muscular dystrophies
• Dystrophinopathies (Duchenne and Becker muscular dystrophy)
• Classic form of congenital muscular dystrophy:
  o With merosin deficiency
  o Without merosin deficiency
• Congenital muscular dystrophy-dystroglycanopathy with central nervous system abnormalities:
  o Walker-Warburg disease
  o Muscle-eye-brain disease
  o Fukuyama disease
  o Congenital muscular dystrophy with cerebellar atrophy/hypoplasia
  o Congenital muscular dystrophy with occipital argyria
• Early infantile facioscapulohumeral dystrophy
• Congenital myotonic dystrophy

Congenital motor or sensory neuropathies
• Charcot-Marie-Tooth disease
  o Congenital hypomyelinating neuropathy
  o Dejerine-Sottas disease
• Hereditary sensory and autonomic neuropathy

Neuromuscular junction disorders
• Transient acquired neonatal myasthenia
• Congenital myasthenia
• Magnesium toxicity
• Aminoglycoside toxicity
• Infantile botulism

Congenital myopathies
• Nemaline myopathy
• Central core disease
- Multiminicore disease
- Centronuclear (myotubular) myopathies
- Congenital fiber type disproportion myopathy

**Metabolic and multisystem diseases**

- Disorders of glycogen metabolism:
  - Acid maltase deficiency
  - Severe neonatal phosphofructokinase deficiency
  - Severe neonatal phosphorylase deficiency
  - Debrancher deficiency
- Primary carnitine deficiency
- Peroxisomal disorders:
  - Neonatal adrenoleukodystrophy
  - Cerebrohepatorenal syndrome (Zellweger)
- Disorders of creatine metabolism
- Mitochondrial myopathies:
  - Cytochrome c oxidase deficiency
The following journal article and provide an excellent synopsis of the approach to the infant with hypotonia and weakness:


Leyenaar *et al* (2005, p339) suggest the following approach to the investigation and diagnosis of hypotonia in infancy.

### History:

- **Prenatal History**: TORCH infections? Drugs or alcohol? Maternal illness? Fetal movements?
- **Neonatal History**: Delivery complications? Premature delivery? Sepsis? Initial presentation of hypotonia?
- **Past Medical History**: History of presenting symptoms? Associated symptoms? Symptoms of systemic disease? Rate of symptom progression?
- **Developmental History**: Delayed milestones attainment? Loss of milestones? Motor, social and language incongruence?
- **Feeding History**: Stamina with feeding? Choking or aspiration? Constipation? Honey or corn syrup?

### General Physical Examination:

- **Head and neck**: Microcephaly? Dysmorphic features? Piosis? Facial expression? Nutritional wasting?
- **Systems**: Cardiovascular findings? Liver enlargement? Splenomegaly? Skeletal abnormalities? Arthrogryposis?

### Neurological Examination:

- **Objective – Localize the lesion.**
  - Cranial nerves: Extraocular movements? Muscles of facial expression? Fasciculations of tongue?
  - Tone: Posture? Horizontal and vertical suspension? Scissoring or spasticity?
  - Strength: Proximal versus distal weakness? Symmetry?
  - Muscles: Atrophy? Symmetry?

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<tr>
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<th>Motor Neuron</th>
<th>Nerve</th>
<th>NM Junction</th>
<th>Muscle</th>
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<td>Tone*</td>
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<td>Reflexes</td>
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<td>Muscle Atrophy</td>
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### Investigations:

- **General Investigations**: TSH, free T4, electrolytes (including calcium)
- **CNS Dysfunction Suspected**: CT/MRI head, consider EEG, consult neurology, and consider karyotype
- **Metabolic Disease Suspected**: Urine and serum amino acids, urine organic acids, blood gas, serum ammonia, liver function tests
- **Lower Motor Neuron Disease Suspected**: Creatine kinase, referral to neurology for specialized tests

Pertinent positives, highlighted in italics, raise suspicion of central nervous system and metabolic diseases. ↑ Increased; ↓ Decreased; CNS Central nervous system; CT Computed tomography; EEG Electroencephalography; MRI Magnetic resonance imaging; NM Neuromuscular; TORCH Toxoplasmosis, other infections, rubella, cytomegalovirus infection and herpes simplex; TSH Thyroid-stimulating hormone.
Dystonia and status dystonicus:

Hyperkinetic disorders are characterized by abnormal excessive involuntary movement that can be:
- Regular and rhythmic (tremor).
- More sustained and patterned (dystonia).
- Brief and random (chorea).
- Jerk-like and temporarily suppressible (tics).

The international consensus committee of movement disorder (Albanese et al, 2013) devised the following definitions regarding dystonia:
- Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
- Dystonic movements are typically patterned, twisting, and may be tremulous.

Status dystonicus (SD)

Status dystonicus (also called dystonic storm) is a rare, potentially life-threatening condition. It is classically described as causing increasingly frequent or continuous severe generalized dystonic contractions (which can be caused by a variety of types of dystonia) that may be refractory to standard medical treatment (Manji et al, 1998). Commonly reported complications include:
- Bulbar weakness.
- Progressive impairment of respiratory function leading to respiratory failure.
- Exhaustion.
- Pain.
- Metabolic derangements including rhabdomyolysis and acute kidney injury.
SD is neurologic emergency and often requires the following urgent actions and treatments (Allen et al, 2014. Jankovic, 2013):

- **Supportive care:**
  - Intravenous fluid hydration
  - Antipyretics and cooling strategies
  - Pain control
  - Monitoring for the development of rhabdomyolysis (eg, creatine kinase, urine analysis, and renal function)
  - Sedation with intravenous midazolam (0.03 to 0.1 mg/kg per hour)
  - Possible mechanical ventilation

- **Specific measures to control the dystonia:**
  - It is first worth trying oral agents if the child is not needing ventilation and is not unstable (often in combination):
    - Trihexyphenidyl
    - Tetrabenazine
    - Baclofen
    - Benzodiazepines
    - Gabapentin (slow acting)
  - For chronic and/or refractory cases, consideration the following treatments as a last resort (often in children who are already profoundly disabled):
    - Intrathecal baclofen
    - Deep brain stimulation of the globus pallidus interna
    - Pallidotomy

**Acute dystonic reaction**

An acute dystonic reaction is a recognized complication of the dopamine receptor-blocking drugs including:

- Antipsychotics (eg, haloperidol, chlorpromazine)
- Antiemetics (eg, phenothiazines, metoclopramide)
- Levodopa
- Anticonvulsants
- Antidepressants (eg, selective serotonin reuptake inhibitors (SSRIs))
- Ergots.

Treatment of acute dystonia with antihistamine or anticholinergic medications is usually rapidly effective (Derinoz et al, 2013. Kanburoglu et al, 2013).

- IV/IM diphenhydramine (1mg/kg per dose, maximum dose 50 mg).
- IV/IM/Buccal Benzodiazepines
- Promethazine or Procyclidine are also sometimes used.

Once the acute dystonic reaction is treated, diphenhydramine is given orally (1.25 mg/kg per dose) every 6 hours for 1-2 days to prevent recurrence. The drug that triggered the acute dystonic reaction should be stopped.

**Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis**

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a neuropsychiatric disorder which was named and fully described in 2007 (Dalmau et al. 2007). It commonly presents with behavioural and psychiatric manifestations, followed by a variety of movement disorders, including (Mohammad et al, 2014):
- Chorea
- Stereotypies particularly affecting the orofacial area
- Dystonia
- Slow tremor (myorhythmia)
- Blepharospasm
- Opisthotonus
- Athetosis
- Ataxia

The condition is mediated by autoantibodies that target NMDA receptors in the brain. Diagnosis is gained through detecting these antibodies. The antibodies can be produced by cross reactivity with NMDA receptors in teratomas, which contain many cell types, including brain cells. For this reason the presence of ovarian teratoma or other benign tumours need to be excluded on MRI (ovarian teratomas can be missed on USS) as their removal can lead to resolution of symptoms. Other autoimmune mechanisms are suspected in patients who do not have tumours.

Brain MRI is abnormal in about half of the patients, but cerebrospinal fluid pleocytosis is found in most cases.

Treatments include:
- Steroids
- Intravenous immunoglobulin
- Plasmapheresis
- Rituximab
- Cyclophosphamide

The following article provides an excellent synopsis of anti-NMDAR encephalitis in children:
## Post Year 2 Module Quiz:

### Regarding acute disseminated encephalomyelitis (ADEM):

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<td>50% of cases of ADEM follow immunization.</td>
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| d) | The immunopathological events leading to ADEM can be divided into two major phases:  
  o Initial T cell priming and activation  
  o Subsequent recruitment and effector phase |
| e) | A febrile illness occurs in 50-75% of children in the 2 weeks prior to the onset of typical neurologic symptoms with neurologic symptoms typically appear >28 days after the infection or vaccination. |

### Regarding dystonia and status dystonicus in children:

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| b) | The international consensus committee of movement disorder (Albanese et al, 2013) describes dystonia as a movement disorder characterized by sustained and classically non-intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. |
| c) | The international consensus committee of movement disorder (Albanese et al, 2013) describes how dystonic movements are typically patterned, twisting, and may be tremulous. |
| d) | The management of life threatening status dystonicus may include:  
  o Intravenous fluid hydration  
  o Antipyretics and cooling strategies  
  o Pain control  
  o Monitoring for the development of rhabdomyolysis (eg, creatine kinase, urinalysis, and renal function)  
  o Sedation with intravenous midazolam (0.03 to 0.1 mg/kg per hour)  
  o Mechanical ventilation |
| e) | An acute dystonic reaction is a recognized complication of the dopamine receptor-blocking drugs including:  
  o Antipsychotics (eg, haloperidol, chlorpromazine)  
  o Antiemetics (eg, phenothiazines, metoclopramide) |
### Post Year 2 Module Quiz Answers:

**Regarding acute disseminated encephalomyelitis (ADEM):**

<table>
<thead>
<tr>
<th>Statement</th>
<th>T/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) ADEM is also known as post infectious encephalomyelitis.</td>
<td>True</td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>True</td>
</tr>
<tr>
<td><em>This is True</em></td>
<td></td>
</tr>
<tr>
<td>b) ADEM is a demyelinating disease of the central nervous system that</td>
<td>True</td>
</tr>
<tr>
<td>typically presents as a monophasic disorder associated with multifocal</td>
<td></td>
</tr>
<tr>
<td>neurologic symptoms and disability.</td>
<td></td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>True</td>
</tr>
<tr>
<td><em>This is True</em></td>
<td></td>
</tr>
<tr>
<td>c) 50% of cases of ADEM follow immunization.</td>
<td>False</td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>False</td>
</tr>
<tr>
<td><em>Under 5% of cases of ADEM follow immunization.</em></td>
<td></td>
</tr>
<tr>
<td>d) The immunopathological events leading to ADEM can be divided into</td>
<td>True</td>
</tr>
<tr>
<td>two major phases:</td>
<td></td>
</tr>
<tr>
<td>o Initial T cell priming and activation</td>
<td></td>
</tr>
<tr>
<td>o Subsequent recruitment and effector phase</td>
<td></td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>True</td>
</tr>
<tr>
<td><em>This is True.</em></td>
<td></td>
</tr>
<tr>
<td>e) A febrile illness occurs in 50–75% of children in the 2 weeks prior to</td>
<td>False</td>
</tr>
<tr>
<td>the onset of typical neurologic symptoms with neurologic symptoms</td>
<td></td>
</tr>
<tr>
<td>typically appear &gt;28 days after the infection or vaccination.</td>
<td></td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>False</td>
</tr>
<tr>
<td><em>A febrile illness occurs in 50–75% of children in the 4 weeks prior to</em></td>
<td></td>
</tr>
<tr>
<td>the onset of typical neurologic symptoms with neurologic symptoms</td>
<td></td>
</tr>
<tr>
<td>typically appear <strong>4-13 days</strong> after the infection or vaccination.</td>
<td></td>
</tr>
</tbody>
</table>

**Regarding dystonia and status dystonicus in children:**

<table>
<thead>
<tr>
<th>Statement</th>
<th>T/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Hyperkinetic disorders are characterized by abnormal excessive</td>
<td>True</td>
</tr>
<tr>
<td>involuntary movement that can be:</td>
<td></td>
</tr>
<tr>
<td>o Regular and rhythmic (tremor).</td>
<td></td>
</tr>
<tr>
<td>o More sustained and patterned (dystonia).</td>
<td></td>
</tr>
<tr>
<td>o Brief and random (chorea).</td>
<td></td>
</tr>
<tr>
<td>o Jerk-like and temporarily suppressible (tics).</td>
<td></td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>True</td>
</tr>
<tr>
<td><em>This is True</em></td>
<td></td>
</tr>
<tr>
<td>b) The international consensus committee of movement disorder</td>
<td>False</td>
</tr>
<tr>
<td>(Albanese et al, 2013) describes dystonia as a movement disorder</td>
<td></td>
</tr>
<tr>
<td>characterized by sustained and classically non-intermittent muscle</td>
<td></td>
</tr>
<tr>
<td>contractions causing abnormal, often repetitive, movements, postures,</td>
<td></td>
</tr>
<tr>
<td><strong>Answer:</strong></td>
<td>False</td>
</tr>
<tr>
<td><em>This is False</em></td>
<td></td>
</tr>
</tbody>
</table>
or both.

**Answer:**
*The international consensus committee of movement disorder (Albanese et al, 2013) describes dystonia as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.*

c) The international consensus committee of movement disorder (Albanese et al, 2013) describes how dystonic movements are typically patterned, twisting, and may be tremulous.

**Answer:**
*This is true.*

d) The management of life threatening status dystonicus may include:
- Intravenous fluid hydration
- Antipyretics and cooling strategies
- Pain control
- Monitoring for the development of rhabdomyolysis (e.g., creatine kinase, urinalysis, and renal function)
- Sedation with intravenous midazolam (0.03 to 0.1 mg/kg per hour)
- Mechanical ventilation

**Answer:**
*This is True.*

e) An acute dystonic reaction is a recognized complication of the dopamine receptor-blocking drugs including:
- Antipsychotics (e.g., haloperidol, chlorpromazine)
- Antiemetics (e.g., phenothiazines, metoclopramide)

**Answer:**
*This is True.*
Appendix 1:

The Academy of Medical Royal Colleges (2008) “A Code of Practice for the Diagnosis and Confirmation of Death” has been condensed by the Faculty of Intensive Care Medicine (FICM) and sections of this are included below:


<table>
<thead>
<tr>
<th>Exclusion of Reversible Causes of Coma and Apnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Test</td>
</tr>
<tr>
<td>Dr One</td>
</tr>
<tr>
<td>Is the coma due to depressant drugs? Drug Levels (if taken):</td>
</tr>
<tr>
<td>Is the patient’s body temperature ≤34°C?</td>
</tr>
<tr>
<td>Is the coma due to a circulatory, metabolic or endocrine disorder?</td>
</tr>
<tr>
<td>Is the apnoea due to neuromuscular blocking agents, other drugs or a non brain-stem cause (eg. cervical injury, any neuromuscular weakness)?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests for Absence of Brain-Stem Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Test</td>
</tr>
<tr>
<td>Dr One Examing</td>
</tr>
<tr>
<td>Do the pupils react to light?</td>
</tr>
<tr>
<td>Is there any eyelid movement when each cornea is touched in turn?</td>
</tr>
<tr>
<td>Is there any eye movement during or following caloric testing in each ear?</td>
</tr>
<tr>
<td>Is there any motor response when supraorbital pressure is applied?</td>
</tr>
<tr>
<td>Is the gag reflex present?</td>
</tr>
<tr>
<td>Is the cough reflex present?</td>
</tr>
<tr>
<td>Arterial Blood Gas pre apnoea test check: (Starting paCO₂ ≥ 6.0 kPa and starting pH &lt; 7.4 or [H⁺] &gt; 40 nmol/L)</td>
</tr>
<tr>
<td>Arterial Blood Gas Result post apnoea test: (paCO₂ rise should be &gt; 0.5 kPa)</td>
</tr>
</tbody>
</table>
The FICM abbreviation of the Code of Practice for the Diagnosis and Confirmation of Death also states:

*It remains the duty of the two doctors carrying out the testing to be satisfied with the aetiology, the exclusion of all potentially reversible causes, the clinical tests of brain-stem function and of any ancillary investigations so that each doctor may independently confirm death following irreversible cessation of brain-stem function.*

The diagnosis of death by neurological criteria should be made by at least two medical practitioners who have been registered for more than five years and are competent in the conduct and interpretation of brain-stem testing. At least one of the doctors must be a consultant. Testing should be performed completely and successfully on two occasions with both doctors present.

Diagnostic caution is advised in the following ‘Red Flag’ patient groups. (Based on the literature and unpublished case reports.)
1. Testing < 6 hours of the loss of the last brain-stem reflex
2. Testing < 24 hours where aetiology primarily anoxic damage
3. Hypothermia (24 hour observation period following re-warming to normothermia recommended)
4. Patients with any neuromuscular disorders
5. Steroids given in space occupying lesions such as abscesses
6. Prolonged fentanyl infusions
7. Aetiology primarily located to the brain-stem or posterior fossa

**Evidence for Irreversible Brain Damage of Known Aetiology**
- There should be no doubt that the patient’s condition is due to irreversible brain damage of known aetiology. Occasionally it may take a period of continued clinical observation and investigation to be confident of the irreversible nature of the prognosis. The timing of the first test and the timing between the two tests should be adequate for the reassurance of all those directly concerned. If in doubt wait and seek advice.

**Children** (one examining doctor should normally be a paediatrician or should have experience with children and one of the doctors should not be primarily involved in the child’s care)
- Older than 2 months: This guideline can be used in children older than 2 months of age.
- Between thirty seven weeks gestation to 2 months of age: given the current state of knowledge, it is rarely possible to confidently diagnose brain-stem death in this age group.
- Infants below 37 weeks gestation: the concept of brain-stem death is inappropriate for infants in this age group.

**Drugs**
- The patient should not have received any drugs that might be contributing to the unconsciousness, apnoea and loss of brainstem reflexes (narcotics, hypnotics, sedatives or tranquillisers). Where there is any doubt specific drug levels should be carried out (midazolam less than < 10mcg/L, thiopentone <5mg/L. Alternatively consider ancillary investigations.
There should be no residual effect from any neuromuscular blocking agents (atracurium, vecuronium or suxamethonium), consider the use of peripheral nerve stimulation.

Renal or hepatic failure may prolong metabolism/excretion of these drugs.

**Temperature, Circulatory, Metabolic or Endocrine Disorders**

- Prior to testing aim for: temperature > 34°C, mean arterial pressure consistently >60mmHg (or age appropriate parameters for children), maintenance of normocarbia and avoidance of hypoxia, acidaemia or alkalaemia (PaCO₂ 10 kPa and pH 7.35 –7.45 / [H+] 45-35 nmoles/L).
- Serum Na+ should be between 115-160mmol/L; Serum K+ should be > 2mmol/L; Serum Phosphate and Magnesium should not be profoundly elevated (>3.0mmol/L) or lowered (<0.5mmol/L) from normal.
- Blood glucose should be between 3.0-20mmol/L before each brain stem test.
- If there is any clinical reason to expect endocrine disturbances then it is obligatory to ensure appropriate hormonal assays are undertaken.

**Brain Stem Reflexes**

- Pupils should be fixed in diameter and unresponsive to light.
- There should be no corneal (blink) reflex (care should be taken to avoid damage to cornea).
- Eye movement should not occur when each ear is instilled, over one minute, with 50mls of ice cold water, head 30 degrees. Each ear drum should be clearly visualised before the test.
- There should be no motor response within the cranial nerve or somatic distribution in response to supraorbital pressure. Reflex limb and trunk movements (spinal reflexes) may still be present.
- There should be no gag reflex following stimulation to the posterior pharynx or cough reflex following suction catheter placed down the trachea to the carina.

**Apnoea Test**

- End tidal carbon dioxide can be used to guide the starting of each apnoea test but should not replace the pre and post arterial PaCO₂.
- Oxygenation and cardiovascular stability should be maintained through each apnoea test.
- Confirm PaCO₂ ≥6.0 kPa and pH < 7.4 / [H+] >40 nmoles/L. In patients with chronic CO₂ retention, or those who have received intravenous bicarbonate, confirm PaCO₂ >6.5 kPa and the pH < 7.4 / [H+] >40 nmoles/L.
- Either use a CPAP circuit (eg Mapleson B) or disconnect the patient from the ventilator and administer oxygen via a catheter in the trachea at a rate of >6L/minute.
- There should be no spontaneous respiration within a minimum of 5 (five) minutes following disconnection from the ventilator.
- Confirm that the PaCO₂ has increased from the starting level by more than 0.5 kPa.
- At the conclusion of the apnoea test, manual recruitment manoeuvres should be carried out before resuming mechanical ventilation and ventilation parameters normalised.
Ancillary Investigations

- Ancillary investigations are NOT required for the diagnosis and confirmation of death using neurological criteria. Any ancillary or confirmatory investigation should be considered ADDITIONAL to the fullest clinical testing and examination carried out to the best of the two doctor's capabilities in the given circumstances.

Organ Donation

- National professional guidance advocates the confirmation of death by neurological criteria wherever this seems a likely diagnosis and regardless of the likelihood of organ donation.
- NICE guidance recommends that the specialist nurse for organ donation (SN-OD) should be notified at the point when the clinical team declare the intention to perform brain-stem death tests and this is supported by GMC guidance.

Appendix 2:
The RCPCH published its guideline on The diagnosis of death by neurological criteria in infants less than two months old April in 2015:

Sections of this guideline and executive summary are included below.

<table>
<thead>
<tr>
<th>Dr A:</th>
<th>Dr B:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset of unresponsive coma:</td>
<td></td>
</tr>
<tr>
<td>Observation period:</td>
<td></td>
</tr>
<tr>
<td>Dr A:</td>
<td>Dr B:</td>
</tr>
<tr>
<td>Are you satisfied that the potentially reversible causes for the patient’s condition have been adequately excluded (Y = excluded; N = not excluded), in particular:</td>
<td></td>
</tr>
<tr>
<td>Dr A:</td>
<td>Dr B:</td>
</tr>
<tr>
<td>Depressant drugs</td>
<td>1st exam</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
<td>2nd exam</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>1st exam</td>
</tr>
<tr>
<td>Metabolic/endocrine disturbance</td>
<td>2nd exam</td>
</tr>
</tbody>
</table>

Tests for absence of brain stem function (Y = present; N = absent): 1st set of tests | 2nd set of tests | 1st set of tests | 2nd set of tests
---|---|---|---
Do the pupils react to light? | | |
Are there corneal reflexes? | | |
Is there eye movement on caloric testing? | | |
Are there motor responses in the cranial nerve distribution in response to stimulation of face, limbs, or trunk? | | |
Is the gag reflex present? | | |
Is there a cough reflex? | | |
Have the recommendations concerning testing for apnoea been fulfilled? | | |
Were there any respiratory movements seen? | | |
Date and time of first set of tests: | Date and time of second set of tests: |
Dr A signature: | Dr B signature: |
Status: | Status: |

**Preconditions**
The working group recommends that the preconditions detailed in the 2008 AoMRC’s Code of Practice, and also expressed in the 1991 BPA report, should be fulfilled before diagnosing DNC:
- The patient is comatose and mechanically ventilated for apnoea.
- The diagnosis of structural brain damage has been established or the immediate cause of coma is known (2008 AoMRC’s Code of Practice2) and, in particular:
  a. Drugs are not the cause of coma;
  b. Neuromuscular blockade has been demonstrably reversed;
  c. Hypothermia does not exist (temperature >34°C);
  d. There is no endocrine or metabolic disturbance that could be the primary cause of the state of unresponsiveness.
The working group considered an extra precondition in this patient population was appropriate:

- In post-asphyxiated infants, or those receiving intensive care after resuscitation, whether or not they have undergone therapeutic hypothermia, there should be a period of at least 24 hours of observation during which the preconditions necessary for assessment for DNC should be present before clinical testing for DNC. If there are concerns about residual drug-induced sedation, then this period of observation may need to be extended.

Clinical diagnosis
The diagnosis of DNC using the clinical examination criteria used to establish death in adults, children and older infants, as outlined in the 2008 AoMRC's Code of Practice, can be confidently used for infants from 37 weeks corrected gestation (post menstrual) to two months post term:

- Absent brain stem reflexes
- Absent motor responses
- No respiratory response to hypercarbia

However in view of the immaturity of the newborn infant's respiratory system, the following precautionary measure should be considered regarding the apnoea test:

- A stronger hypercarbic stimulus is used to establish respiratory unresponsiveness. Specifically, there should be a clear rise in the arterial blood partial pressure of carbon dioxide (PaCO₂) levels of >2.7 kPa (>20 mm Hg) above a baseline of at least 5.3 kPa (40 mm Hg) to >8.0 kPa (60 mm Hg) with no respiratory response at that level.

The interval between tests need not be prolonged as stated in the 2008 AoMRC's Code of Practice.

Ancillary tests
Ancillary tests are not required to make a diagnosis of DNC in infants from 37 weeks corrected gestation (post menstrual) to two months post term.
### References: (pooled from module 44a&amp;b)


• Dalmau, Josep; Tüzün, Erdem; Wu, Hai-yan; Masjuan, Jaime; Rossi, Jeffrey E.; Voloschin, Alfredo; Baehring, Joachim M.; Shimazaki, Haruo; Koide, Reiji; King, Dale; Mason, Warren; Sansing, Lauren H.; Dichter, Marc A.; Rosenfeld, Myrna R.; Lynch, David R. 2007. "Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma". Annals of Neurology 61 (1): 25–36.


• Fischer, M; Rüegg, S; Czapinski, A; Strohmeier, M; Lehmann, A; Tschan, F; Hunziker, PR; Marschcorresponding, SC. 2010. "Inter-rater reliability of the Full Outline of UnResponsiveness score and the Glasgow Coma Scale in critically ill patients: a prospective observational study". BioMed Central: Critical Care 14 (2): R–64.


