Neuromuscular conditions

Organ specific problems

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Weakness may precipitate Intensive Care Unit (ICU) admission, and can result from generalised disease states (such as malnutrition), critical illness (such as severe sepsis) or those specific states which primarily affect the neuromuscular system e.g. myasthenia gravis, Guillain-Barré Syndrome (GBS). Weakness may result from impacts on upper or lower motor neurones (in isolation or with involvement of other peripheral or central nervous system elements), motor end plates (neuromuscular transmission), or skeletal muscle itself. Whatever the cause, ICU admission related to such conditions generally results from respiratory muscle weakness and/or difficulty in swallowing, with consequent aspiration. Early recognition and intervention is crucial: death can result from ventilatory failure and/or aspiration pneumonia, and the autonomic instability which complicates some conditions.

Neuromuscular conditions can also complicate critical illness, increasing the duration of mechanical ventilation and of ICU and hospital stay, and causing post-discharge morbidity and mortality.

You will find the following references helpful in understanding the broad range of neuromuscular conditions encountered in the ICU.


This should focus on four elements:
1. Determining the severity of weakness
2. Characterising involvement of bulbar muscles (and thus risk of aspiration)
3. Characterising involvement of respiratory muscles
4. Determining the cause, such that appropriate treatment can be instigated.

Determining the severity of weakness

Specific patterns of weakness should be sought (proximal myopathy, nerve distribution, cord level). Gait should be routinely assessed where practical and possible e.g. when considering patients for ICU admission prior to high-risk surgery. Of note, weakness can change rapidly in some conditions (see GBS, Task 3), and can also change with time of day or activity (see, for example, myasthenia gravis, Task 3). Repeated and sometimes frequent examination, sometimes with provocation testing, may thus be required.

Characterising bulbar involvement

Is there a history of change in voice or phonation? (Note: a hoarse voice may suggest recurrent laryngeal nerve involvement, or may suggest chronic aspiration). Is swallowing harder? Does eating result in coughing? Ask about specific food types (as semi-solids may be easier to swallow than thin liquids). Is there nasal regurgitation? Ask about features related to brainstem function/function of other cranial nerves, and perform appropriate examination, seeking palatal deviation on swallowing or on phonation, and tongue deviation on protrusion. Also seek evidence of tongue fasciculation (see motor neurone disease, Task 3). Assess glottic closure by having the patient perform a cough.

Characterising respiratory muscle involvement

Clinical assessment

The respiratory muscles fall into three groups.
(i) The diaphragm (supplied by C3,4,5 roots) is active only in inspiration. Normal inspiration causes flattening of the diaphragm, and the abdomen below the ribs to bulge out. Failure for this to happen may suggest diaphragmatic paresis. Further, indrawing of the upper abdomen during inspiration (paradoxical movement) may also be observed in such circumstances.
(ii) The intercostal muscles (supplied by T1-12 nerve roots) are involved in inspiration, and in forced or active expiration. On inspiration, ribs 1-6 move anteriorly and ribs 7-10 laterally. The magnitude of this change should be assessed. Cord compression may cause paralysis of these muscles below that level, and the rib cage will move inwards paradoxically during rapid nasal inspiration (under the influence of the negative intrathoracic pressure generated by the inspiration).
(iii) Accessory muscles of inspiration (such as sternocleidomastoids and latissimus dorsi). Each component should be assessed, and appropriate causes of the pattern of weakness identified.
Use of accessory muscles and nasal flaring may represent a high work of breathing, or ‘air hunger’ where ventilation is inadequate through weakened musculature. In the latter case, tidal volumes (Vt) may fall, and ventilatory rate (f) may rise - causing their ratio (f/Vt, the ‘rapid shallow breathing index’ which is normally <50/min/L) to increase. Ventilatory failure, by causing PaCO₂ to rise, may lead to restlessness and thence to a fall in conscious levels.

**NOTE** In patients on ventilatory support, reducing the level of pressure support (perhaps to zero) or a spontaneous breathing trial (SBT) for a diagnostic period may help reveal patterns of weakness.

**WARNING** Arterial blood gases are an extremely unreliable indicator of respiratory strength or the need for mechanical ventilation in neuromuscular disorders. Patients with rapid shallow breathing should be closely monitored even if blood gases are normal.

### Additional tests

Information gained from clinical assessment is essential but can be further substantiated through the use of **spirometry**. Maximal negative inspiratory force (an index of inspiratory muscle function) and maximal expiratory force (reflecting force of cough) can be measured by trained specialists using an electronic strain gauge attached to a mouth piece. More usefully, Forced Vital Capacity (FVC) assesses composite inspiratory and expiratory force and lung volume and is easily performed at the bedside with minimal training. FEV₁ (the volume expired in 1 second of forced expiration) and peak expiratory flow rate (PEFR) offer composite indices of expiratory muscle force and airway resistance (note - they will be NORMAL in GBS). In patients where disease progression may lead to respiratory failure, spirometry should be performed at appropriate (and responsively changing) intervals. An FVC of <1 L, or a decline of more than 50% from baseline and maximal inspiratory force less negative than – 20 cmH₂O should lead to urgent consideration of mechanical ventilatory support in GBS.

See Vital Capacity in PACT module on Respiratory assessment and monitoring.

**NOTE** FVC is easy to perform at the bedside, but it is nonspecific diagnostically. Thus, normal FVC excludes moderate to severe respiratory muscle weakness, but reduced FVC can be due to respiratory muscle weakness, or pulmonary disease, or both.

**NOTE** A rough estimate of the Forced Vital Capacity can be obtained by asking the patient to count to 20 after taking a single breath: inability to do so corresponds to a greatly reduced vital capacity in the order of 15-18 mL/kg (normal values are 65-75 mL/kg).

Assessment of **arterial blood gases** may also be of value. Note that oxygenation (whether through monitoring of arterial oxygen saturation or PaO₂) is not an index of ventilation, and measurements will only fall when PaCO₂ is rising dangerously (in compliance with the alveolar gas equation). Otherwise, the presence of hypoxaemia
points to other pathologies which have resulted in Ventilation/Perfusion mismatch e.g. atelectasis, aspiration (where, for instance, bulbar muscle function is also impaired) or pulmonary embolus due to immobility.

The magnitude of hypercarbia reflects limitations in ventilation of functional alveoli (reduced overall ventilation, or increased physiological deadspace, or both). The resulting respiratory acidaemia may be metabolically compensated, if of sufficient duration.

Q. Why are blood gases maintained in neuromuscular weakness until respiratory arrest?

A. As tidal volume decreases because of muscle weakness, respiratory rate increases to maintain minute ventilation. Arterial blood gases are maintained within the normal ranges, or arterial oxygenation is slightly reduced because of impaired cough and microatelectasis. Eventually the respiratory rate cannot be sustained, hypercapnia develops and respiratory arrest supervenes.

The following reference addresses respiratory muscle testing in the non-intubated patient in greater detail:


Clinical examination of respiratory muscle function in the conscious intubated patient should follow the pattern outlined above in the conscious patient. Whether conscious or not, f/Vt ratio may be high in those with respiratory muscle weakness and has been used to predict successful extubation although poor sensitivity and specificity limit this role. Diaphragm strength can be evaluated objectively using phrenic nerve stimulation in conjunction with oesophageal manometry, although this is technically difficult, expensive and only available in specialist centres.

Maximal Inspiratory Pressure (MIP), Maximal Expiratory Pressure (MEP) and Forced Vital Capacity (FVC) can be measured in cooperative patients by disconnecting them from the ventilator, and performing a manual occlusion in inspiration (MIP) or expiration (MEP). Again, these tests are mainly used in clinical research rather than to guide management. Expiratory muscle strength can be evaluated using cough peak flow in intubated patients - values of 35-60 L/min being described as thresholds for successful extubation. These tests are exclusively clinical and based on subjective evaluation, therefore their generalised application and interpretation are limited by the need for patient awareness and co-operation.

In patients who develop muscle weakness on the ICU (Intensive Care Acquired Weakness, ICU-AW), peripheral muscle weakness is paralleled by respiratory muscle weakness. ICU-AW is diagnosed by the use of the Medical Research Council Sum Score (MRC-55, figure below). An arbitrary score of 48 is used as a diagnostic cut-off for ICU-AW. The clinical utility of the MRC-55 is limited in the ICU - over 30-40% of patients are unable to reliably perform the required tests at awakening, and there are concerns regarding inter-rater reliability. Handgrip strength has also been shown to be useful in the diagnosis of ICU-AW, but similarly needs an awake, cooperative patient.
Medical Research Council Sum Score as described by Kleyweg et al in 1991. This has been adapted for use within the ICU, with an arbitrary cut-off of 48 used to define ICU-AW.

**NOTE** Use of the MRC requires an awake and fully cooperative patient. Patients with sedation or delirium may not be assessable.

For further reading:


Patel KN, Ganatra KD, Bates JH, Young MP. Variation in the rapid shallow breathing index associated with common measurement techniques and conditions. Respir Care 2009; 54(11): 1462-1466. PMID 19863829


Q. What are the clinical signs indicating a bulbar involvement in patients with muscle weakness?

A. Reduced cough strength, difficulty in swallowing, deviation of the tongue on protrusion, or a change in the voice are common signs indicating bulbar or cranial nerve involvement.

Q. Why are signs of cranial nerve involvement important to detect in patients with muscle weakness.

A. Protective pharyngeal reflexes can be reduced in these patients, and the risk of inhalation of gastric content or oral secretions is greatly increased.

Q. How can the respiratory muscle strength be assessed in mechanically ventilated patients with suspected respiratory muscle weakness?

A. Inspiratory and expiratory muscle strength can be assessed by measuring the Maximal Inspiratory Pressure (MIP), the Maximal Expiratory Pressure (MEP) and Forced Vital Capacity (FVC). MEP and MIP can be measured after a forced expiration and a forced inspiration respectively, against a manual occlusion of the respiratory circuit. Forced Vital Capacity (FVC) can be easily measured at the bedside using a spirometer.

Determining the cause of weakness

Clinical assessment

History and clinical examination should help localise the pathogenic origin of weakness to upper and lower motor neurones, neuromuscular junctions or to skeletal muscle itself (see below). Signs will vary depending on the anatomical localisation of the lesion, and whether it is acute or chronic. Specifically, note that acute spinal
damage (of whatever cause) can lead to flaccid limbs with ‘pathological down going plantars’, despite their ‘upper motor neurone’ aetiology. A clinical examination that reveals symmetrical signs, mixed motor and sensory deficits or mixed upper and lower motor neuron signs, or a sensory level mandates urgent exclusion of spinal pathology.

Standard textbooks of clinical examination and clinical signs may be used to refresh knowledge of neurological examination and lesion localisation but the table below summarises the process of lesion localisation (upper motor, lower motor, neuromuscular junction or muscle lesion) on the basis of the clinical signs.

### Classical localising signs in neuromuscular disease

<table>
<thead>
<tr>
<th>Site</th>
<th>Upper Motor Neuron</th>
<th>Lower Motor Neuron</th>
<th>Neuromuscular Junction</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal signs</td>
<td>Present</td>
<td>Absent (usually)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Tone</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Increased (+clonus)</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensation</td>
<td>May be altered</td>
<td>May be altered</td>
<td>Unaltered</td>
<td>Unaltered</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>Late wasting: Arms: Extensor&gt;Flexor</td>
<td>Early wasting</td>
<td>Late wasting</td>
<td>Varied pattern (proximal most common)</td>
</tr>
<tr>
<td></td>
<td>Legs: Flexor&gt;Extensor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Babinski and Hoffman signs</td>
<td>Fasciculation</td>
<td>Fatigability may be present</td>
<td>Muscle pain</td>
</tr>
</tbody>
</table>

**THINK** Remember that the appearance of focal neurological deficits (i.e. monoparesis, hemiparesis) should always suggest a central nervous system complication, such as acute brain ischaemia or haemorrhage.

**THINK** Remember that intact sensation suggests an alteration of the neuromuscular transmission, as in myasthenia gravis, or a myopathic process.

**NOTE** Systemic and upper motor neuron diseases cause limb muscle weakness, not respiratory muscle weakness.

### Laboratory investigations

Most neuromuscular conditions are not associated with pathognomic abnormalities on routine blood investigation. Serum myoglobin and creatine kinase (CK) activity are elevated in rhabdomyolysis and many myopathies. Gross elevation suggests widespread destruction of muscle (as in rhabdomyolysis, polymyositis, and some of the muscular dystrophies). Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein suggests an inflammatory process, although sepsis would need to be excluded. Urine dipstick may be positive for blood if myoglobin is present (they cross-react) as a result of rhabdomyolysis, although this is not a sensitive test (up to 50% can be negative in myoglobinuria). Specific antibody tests may assist (e.g. anti-acetylcholine receptor antibodies in myasthenia gravis; anti-synthetase in
polymyositis; anti-ganglioside and voltage-dependent potassium channels in motor neurone disease; anti-Ro, anti-La, anti-Sm, or anti-ribonucleoprotein (RNP) antibodies in mixed connective tissue disease).

**Radiological investigations**

Techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) may help localise and define the causes of upper and lower motor neurone lesions - for instance cord compression, transverse myelitis, extradural abscess, and demyelination. Specific angiography might be urgently required to exclude vascular causes. Rapid diagnoses (or exclusion) of these processes may be mandatory in the acute setting.

**Cerebrospinal fluid analysis**

With raised intracranial pressure appropriately excluded, analysis of cerebrospinal fluid can prove helpful. In GBS, raised protein content (0.5-2.0 g/L) with no increase in cells characteristically present in over 90% of patients two weeks post-onset, but needs to be differentiated from other causes of high CSF protein (such as tuberculosis, neurosarcoidosis and malignancy). A white cell count of >5 cells/mm³ may suggest an infective cause (tuberculosis, polio, encephalitis, extradural abscess or transverse myelitis), or a haematological malignancy.

**Skeletal muscle biopsy**

If prognosis is uncertain, muscle biopsy may be helpful, as patients with thick-filament myopathy (i.e. a myopathy where only the myosin filaments are lost) have a good prognosis. Muscle biopsy may also be indicated when concerns exist of a rare underlying myopathy (leading to weakness, and thus ventilator dependence).

**Sleep studies**

While hypercarbia may be a sign of respiratory muscle weakness, so too may it be a sign of reduced respiratory drive or of an increase in physiological deadspace. Sleep studies can be useful in differentiating these, and in the specific diagnosis of sleep-related disorders. The apnoea-hypopnoea index (AHI) is a measure of the total number of episodes per hour of sleep in which breathing ceases or is partially obstructed. Each episode must last >10 seconds, and must be associated with arterial deoxygenation. Nocturnal hypercapnia can be the first presentation of type II respiratory failure in Chronic Obstructive Pulmonary Disease. Finally the presence of nocturnal hypoventilation in chronic neuromuscular diseases is a marker of disease progression, and the need for both domiciliary non-invasive ventilation and for multidisciplinary discussions regarding future intubation and ventilation. The presence of a severe sleep disorder should prompt right heart investigations, as cor pulmonale requires specific management in critically ill patients.

Apnoea-hypopnoea index (AHI) values are typically categorised as mild (5-15/hr); moderate (15-30/hr) and severe (>30/h). A severe AHI (or >20% sleep time spent with SaO₂ <90%) indicates a high risk of a ‘difficult airway’ and of post-operative respiratory failure.
Neurophysiological studies

Nerve conduction studies
These can measure nerve conduction velocity and nerve action potential amplitude. Sensory nerves are evaluated by stimulating them while recording the transmitted action potential. Motor nerves are evaluated by stimulating them while recording the compound muscle action potential from the innervated muscle. Slowed nerve conduction occurs when nerves are demyelinated, the most common cause in the ICU patients being the acute inflammatory demyelinating subtype of the Guillain-Barré syndrome.

Compound muscle action potential (CMAP)
Reduction in amplitude suggests an axonal motor neuropathy. If associated with increase in duration, it suggests a myopathy.

Sensory nerve action potentials (SNAP)
Reduction suggests an axonal sensory neuropathy.

Repetitive stimulation
A 10% decrement suggests neuromuscular failure due to persistence of neuromuscular blocking agents (NMBAs) or myasthenia gravis. It may also be used to monitor the response to edrophonium in myasthenia gravis.

Electromyography (EMG)
EMG is the electrophysiological examination of muscle. At rest (no patient collaboration required), EMG may show abnormal muscle electrical activity such as fibrillation potentials or positive sharp waves suggesting muscle denervation (the normal response after needle insertion into the muscle is electrical silence). With minimal voluntary muscle contraction (patient’s collaboration required), EMG may show low amplitude, short-duration, polyphasic motor unit potentials indicating myopathy, or large amplitude, long-duration, polyphasic motor unit potentials indicating neuropathy. With maximal voluntary contraction, EMG may show single oscillations or transitional pattern indicating neuropathy, or normal interference pattern. Therefore, EMG can differentiate myopathy from neuropathy if the patient is able to collaborate with testing.

Single-fibre electromyography (SFEMG)
When a motor axon is depolarised, the action potentials travel distally and excite the muscle fibres at more or less the same time. SFEMG is a selective EMG recording technique that allows the measurement of the variability in the arrival time of action potentials belonging to the same motor unit to the micro-recording electrode. Increased variability (jitter) reflects defective neuromuscular transmission, and is most valuable in the patient with suspected myasthenia gravis (see Task 3).

Direct muscle stimulation (DMS)
In DMS, both the stimulating and the recording electrodes are placed in the muscle distal to the end-plate zone. A patient with neuropathy will have a reduced or absent action potential when using conventional stimulation (i.e. through the motor nerve), but normal action potential when using DMS; in case of myopathy, the action potential will be reduced or absent after both conventional stimulation and DMS.

Nerve conduction studies and electromyography can be useful in patients who do not respond to initial treatment, or in whom prognosis is uncertain - see Critical Illness
Polyneuropathy (CIP) and Critical Illness Myopathy (CIM) and the Patient Challenges.

Neurophysiological testing is also essential for the diagnosis of peripheral nerve injury - both foot drop and entrapment syndromes are common and, untreated, lead to functional disability. Further it can be used to distinguish other less common causes of weakness (detailed below) that are unmasked by critical illness (e.g. motor neurone disease).

Therefore, nerve conduction studies should be carried out when clinically indicated:
- On clinical diagnosis of a peripheral nerve lesion
- When weakness occurs acutely, and the diagnosis is unclear (or for confirmation of diagnosis)
- To investigate weakness noted late in the course of disease if clinically not in keeping with ICU-AW
- If ICU-AW does not improve despite rehabilitation.


Q. How is the ICU-acquired weakness assessed in the ICU?

A. The Medical Research Council (MRC) Sum Score is commonly used to evaluate muscle strength clinically. An MRC of less than 48 identifies patients with severe muscle weakness.

Q. The pattern of distribution of muscle weakness is typical in patients with ICU-acquired weakness. Can you describe the main features and their implication for the differential diagnosis?

A. Although there is some evidence of a proximal preponderance, muscle weakness is symmetrically and diffusely distributed in both lower and upper arms. Commonly however, it is more severe in the lower limbs. If muscle weakness is limited to a single limb, other causes should be sought e.g. entrapment neuropathy.

Consider discussing with the Critical Care senior staff the routine implementation of limb and respiratory muscle strength evaluation in patients with suspected neuromuscular disorders. If agreed, contact your hospital’s neurophysiology department and discuss the possibilities of undertaking such studies in the ICU starting with a representative critically ill patient.
A 47-year-old man with a history of diabetes was noted to have altered ambulation with a steppage gate pattern during rehabilitation after a three-week ICU stay for community-acquired pneumonia and acute respiratory failure. Physical examination showed severe muscle wasting, and ankle dorsiflexion weakness at the left leg. Nerve conduction study eventually diagnosed a left peroneal nerve palsy. Mechanisms of nerve injury in the ICU can be multifactorial (fractures, plasters, surgery) and can remain undetermined. Since peroneal nerve injuries usually occur at the region of the fibular head, rapid muscle wasting resulting in loss of the fat pad over the fibular head may predispose to nerve injury. Compression of the nerve against a bed railing may cause nerve injury, and is easily avoided with careful attention to the patient’s positioning in the bed.
2/ General Issues in the Management of the Patient with Neuromuscular Disease

The evidence base underpinning the general ICU management of neuromuscular disease (NM) is limited.

Predicting acute respiratory failure

The majority of the data regarding prediction of acute respiratory failure in neuromuscular disease relate to GBS patients, amongst whom hourly measurements of respiratory function should be performed by competent staff. The presence of facial weakness may make it impossible to perform measurement of FVC, and is a strong predictor of the need for future intubation. The following parameters have been demonstrated to predict imminent respiratory failure in GBS, and mandate transfer to the ICU for consideration of elective intubation. Such values might pragmatically be applied to other neuromuscular conditions, albeit without a strong evidence base to support this:

- FVC of <20 mL/kg or a rapid decline
- Maximum Inspiratory Pressure <30 cmH₂O
- Maximum Expiratory pressure <40 cmH₂O

Clinical features can also highlight those at risk of respiratory failure in GBS:
- Time of onset to admission less than seven days
- Presence of bulbar dysfunction
- Low Medical Research Council (MRC) score at admission
- Inability to cough
- Inability to stand
- Inability to lift the elbows
- Inability to lift the head.

THINK Proper diagnosis requires accurate consideration of the patient’s clinical history, as the same pattern of neurophysiological abnormalities (of peripheral nerves and muscles) may characterise different diseases.

For further reading:


**Airway protection and secretion management**

The indications for intubation are worsening spirometry, failing CO$_2$ clearance, inability to manage secretions and the risk of aspiration (worsening swallow or speech). Particular attention is paid to bronchopulmonary toilet, as secretions may be increased (e.g. by anticholinesterase treatment in myasthenia gravis) or difficult to clear due to ineffective cough, causing pneumonia or atelectasis. In intubated patients, subglottic secretion drainage may be of use here, as it has been shown to decrease the incidence of ventilator-acquired pneumonia in a general ICU population.

**Q. Why are oral hygiene and bronchopulmonary toilet important in patients with NM disease?**

A. Secretions may accumulate in the oral cavity because some drugs used in the treatment of the NM disease have anticholinesterase effects, and patients may be unable to swallow their secretions. As infections of the lower respiratory tract are preceded by colonisation or infection of the upper airway, the risk of micro- or macro-aspiration of infected secretions from the upper airway is increased in these patients. Moreover, the epiglottis can be partially or completely incompetent in protecting the airway, further favouring the inhalation of secretions and pneumonia.

**Ventilation and weaning**

Respiratory weakness generally results in reduced tidal volumes and an increase in respiratory rate (see f/Vt, above). Higher inspiratory flow rates and levels of pressure support may be needed in spontaneous modes of ventilation to prevent air hunger; also the ventilator trigger sensitivity should be assessed as there may be insufficient patient-generated inspiratory pressure to trigger the ventilator. Neurally Adjusted Ventilator Assist (NAVA) may have a role as in this circumstance, triggering is not based on flow, but on diaphragm electrical activity. Weaning can only occur in the context of improving neuromuscular function. In a series of 44 patients with...
Guillain–Barré Syndrome, the best predictor of successful weaning was an increase of 4 mL/kg in vital capacity from pre-intubation values. In most NM diseases, active pulmonary pathology (infection, atelectasis) or autonomic instability greatly increases the risk of extubation failure.

Q. Given that ventilator-associated pneumonia (VAP) and atelectasis are frequent complications in patients with NM disease in the ICU, explain how the chest X-ray may be useful in patient management?

A. VAP can be suspected if new infiltrates appear on chest X-ray. Lobar atelectasis can also be diagnosed with chest X-ray showing increased opacification of the airless lobe, displacement of hilar, cardiac and mediastinal structures toward the side of collapse and elevation of the ipsilateral hemidiaphragm.

See the PACT modules on Mechanical ventilation and Clinical imaging.

**Nutrition**

Both the nutritional needs and the mode of delivery need to be assessed. Inadequate nutrition may have led to weakness (e.g. via skeletal muscle wasting, or vitamin D deficiency). Neuromuscular disease may also impair swallowing or gastrointestinal motility (e.g. autonomic dysfunction secondary to Guillain–Barré syndrome, tetanus). In the context of pharyngeal dysfunction, oral intake may have to be avoided. If gastroparesis is present, jejeunostomy and jejunal feeding is recommended in order to avoid as far as possible the use of parenteral feeding. On extubation, poor cough and reduced pharyngeal strength can place patients at risk of aspiration, and this needs to be proactively assessed.

**NOTE** The insertion of feeding tubes that terminate beyond the pylorus, in the first or second part of the duodenum, may overcome the problem of altered gastric motility, and may reduce the risk of pulmonary aspiration in patients with severe gastroesophageal reflux and oesophagitis.

See the PACT modules on Mechanical ventilation and Nutrition.

You might like to talk to your hospital’s gastroenterologists to define the best nutritional approach to patients with difficulty in gastric feeding delivery.

**Thromboprophylaxis**

All patients who suffer from neuromuscular diseases are at greater risk of deep vein thrombosis compared to many other critically ill patients, despite thromboprophylaxis. Some clinicians advocate full anticoagulation, although there is little evidence for this and the opportunity for harm is present. Low molecular weight subcutaneous heparin should be used and mechanical prophylaxis may be additionally considered.
NM diseases may cause prolonged immobility, increasing the risk of deep venous thrombosis. Thromboprophylaxis is indicated in such cases.

Low molecular weight heparin, fondaparinux, or other antithrombotic agents which are primarily cleared by the kidneys should be used with caution in patients with acute kidney failure. A decrease in the usual dose of the drug or use of an alternative form of thromboprophylaxis may be required.

**Sedation and mobilisation**

Mobilisation may be complicated by postural hypotension as a result of autonomic dysfunction, and therefore early mobilisation may not be practical. The importance of postural alterations in ventilation/perfusion matching is increased, and care should be taken to ensure the optimum amount of time is spent sitting up or out of bed. In critically ill patients, protocolised sedation to achieve light sedation can minimise the total dose of sedatives and analgesics without increasing delirium and post-traumatic stress disorder (see also the PACT module on Sedation and Analgesia). In these patients, who are committed to a significant period of ventilation, the additional benefit of regular physiotherapy requires consideration. Passive movement maintains muscle architecture (but not muscle bulk), and helps prevent contractures. Foot drop is common and is treated with specific splints.

**Q. Mobilisation can be of value in speeding the patient’s functional recovery but postural changes may cause hypotension. How can you manage this problem?**

A. Postural manoeuvres can be impractical in patients with severe autonomic dysfunction and are better delayed until the patient’s medical and neurological condition stabilises.


Discuss with the ICU physiotherapist the best strategy to maintain a physical activity in patients with autonomic dysfunction.

Discuss with the nursing staff how to implement a nurse-directed protocol targeting light sedation.
A 43-year-old previously healthy man was diagnosed with GBS characterised by a progressive ascending paralysis requiring mechanical ventilation. He was fully awake and oriented in time and place, and tolerated well the oral tracheal tube with no need for sedation. On day three, he became confused and agitated. Blood chemistry showed progressive reduction of serum sodium from 139 mmol/L to 112 mmol/L. The electrolyte profile was consistent with SIADH, with a low serum sodium and osmolality, and increased urine sodium concentration and osmolality with normal volemia. Fluid restriction and hypertonic saline administration corrected the ionic abnormality, and the patient regained normal mental status. Hyponatraemia may cause brain oedema, and should be actively sought in GBS.

See the PACT module on Electrolytes and Homeostasis (hypo and hypernatraemia).
Guillain-Barré syndrome (GBS)

GBS is an acute autoimmune demyelinating motor polyneuropathy often preceded by an infection, a flu-like episode or gastroenteritis. It is characterised by an ascending symmetrical limb weakness (often beginning in the legs), accompanied by absent tendon reflexes, paresthesia, numbness and sometimes pain. In one third of patients, symptoms involve the four limbs simultaneously, and in 12% progression can be from the upper to the lower limbs. Facial muscles are frequently involved, an important differential criterion from critical illness polyneuropathy (see Task 4). Very occasionally, autonomic dysfunction (detailed below) is the presenting complaint.

In addition, the most common variant form is acute inflammatory demyelinatingpolyradiculoneuropathy (AIDP), but others include the axonal variants (acute motor axonal neuropathy, AMAN; acute motor and sensory axonal neuropathy, AMSAN) and Miller Fisher’s syndrome (MFS). MFS classically presents with ophthalmoplegia, areflexia and ataxia, and 25% also develop limb muscle weakness. GBS usually progresses over several weeks, and by four weeks, the majority of patients will have their severest manifestations.

Diagnosis

Diagnosis of GBS comes from the clinical features (which are important in distinguishing variants) and from cerebrospinal fluid (CSF) examination and neurophysiological studies. The latter are necessary as the differential diagnoses are extensive, and include lesions affecting the cerebellum, compressive/infective/inflammatory myelopathies, toxic neuropathies, and metabolic myopathies.

CSF protein content is typically elevated with a normal white cell count, although this can be normal in the first week. At lumbar puncture, bacterial and viral meningitis should be excluded. The presence of >5 white cells/mm³ CSF, a sensory level or persistent asymmetrical weakness calls the diagnosis of GBS into doubt (see Task 1, cerebrospinal fluid analysis). Neurophysiological investigations are of primary importance not only to achieve a proper diagnosis (i.e. axonal neuropathy versus demyelination) but in gauging response to treatment (using serial measurements) and in prognostication.

Q. Given that CSF protein concentration in patients is often normal in the first week of GBS, what is the value of lumbar puncture in diagnosing GBS?

A. GBS is diagnosed clinically. The CSF protein is increased in more than 90% of the patients at the end of the second week. Therefore, the lumbar puncture is not indicated in the initial diagnostic workup unless other diagnoses must be excluded.
Q. Are neurophysiological studies of the peripheral nerves useful in patients with suspected GBS?

A. Repeated neurophysiological studies are extremely important in differentiating the various sub-types of the syndrome (i.e. demyelinating versus axonal), and in gaining prognostic information.

Q. Does the differentiation of inflammatory from non-inflammatory muscle damage influence therapy?

A. Steroids may be used if there is evidence of muscle inflammation, sometimes with dramatic effect.

Pathology

GBS is an autoimmune, acute peripheral neuropathy which is often preceded by an infection, whose signs (fever) have subsided (to a symptom-free interval) by the time the neurological signs and symptoms start - often described as a 3-phase evolution of disease.

Q. Can you provide a mechanistically plausible explanation for this 3-phase pattern?

A. Infection sets the scene for an aberrant autoimmune response to develop. The symptom-free interval is thought to serve for the autoimmune response to mount (autoantibodies against various gangliosides, activation of T cells, complement and macrophages). Finally, the activated macrophages invade the Schwann cell, the myelin sheath or the nodes of Ranvier, causing nerve damage.

Specific treatment

These are plasma exchange and intravenous immunoglobulin. While plasma exchange improves muscle strength and decreases ventilator dependency, it requires specialist staff. On the other hand, the administration of intravenous immunoglobulin is as effective. Plasma exchange may be superior to intravenous immunoglobulin in patients with acute respiratory failure requiring mechanical ventilation. Glucocorticoids are ineffective in the treatment of GBS.

Q. Is a timely diagnosis of GBS important to its optimum management?

A. Yes. GBS is amenable to specific treatments, which should be started at an early stage to achieve maximum benefit.

For further information:

Controlling autonomic instability

There is often a sinus tachycardia, and blood pressure may fluctuate spontaneously, with postural hypotension a particularly prominent feature. Dramatic autonomic features may be precipitated by tracheal suction: sinus bradycardia, and even asystole, may occur (and a need for temporary cardiac pacing has been described). Drugs with an effect on autonomic nerve function (such as cisapride and metoclopramide) should be used with caution in GBS.

Cardiovascular complications of GBS may be life-threatening.

Pain control

There may be exquisite muscle tenderness, particularly as the patient is recovering. This can be very distressing for the patient and staff, particularly because it is difficult to treat. Gabapentin and Carbamazepine have been used in both the acute and long-term settings. Morphine is effective in the short term but is practically difficult to use well in the context of autonomic instability.

Prognosis

Approximately 20% of patients with GBS require mechanical ventilation. Up to 5% die (from infection, haemodynamic instability or thromboembolic complications), but 85% recover to near-normality.

Botulism

Clostridium botulinum is found in soil, and may contaminate food - the result of careless processing or preserving. The organism can contaminate wounds. It may also be introduced as a result of soil or bone-meal contamination of drugs such as heroin (usually introduced when drugs are ‘cut’ with other substances) injected subcutaneously or intramuscularly (‘skin-popping’ and ‘muscle-popping’).

Pathology

The organism produces neurotoxins, types A, B, E, and (rarely) F which interfere with the production or release of ACh and cause neuromuscular blockade and flaccid paralysis in humans. Symptoms appear six hours to eight days after ingestion of food-source toxin, or four to 18 days after wound contamination (due to the time taken for local toxin synthesis). Wound and food botulism are similar clinically in all other respects except for the lack of gastrointestinal symptoms in wound botulism. Inhalational botulism has been described in laboratory workers or after deliberate dissemination of botulinum.
**Diagnosis**

Further to the history, the four cardinal clinical features are:
- Symmetrical descending neurological manifestations
- Intact mental processes
- Lack of sensory impairment, although vision may be affected due to extra-ocular muscle involvement
- Absence of fever (unless secondary complications are concurrent).

Microbiological diagnoses via serum and wound toxin assays are not always reliable, despite their *in vitro* sensitivity.

**Specific therapies**

Patients receiving specific anti-toxin early have shorter ventilator times and hospital stays. Wound debridement is mandatory to remove toxin and spores. The clinical course is shortened by early treatment.

For further information:


**Tetanus**

Tetanus is caused by *Clostridium tetani*, the spores of which are present in soil. In the United Kingdom, 15-20 cases of tetanus are reported per year. Mortality in the developed world is less often secondary to acute respiratory failure than to sepsis or autonomic instability (and thus cardiac death).

**Pathological features**

Once the organism enters tissue (usually via wounds), it releases tetanospasmin, a neurotoxin affecting inhibitory synaptic vesicle release. The time from inoculation with *C. tetani* to the first symptom can be as short as 24 hours or as long as many months, reflecting the distance the toxin must travel within the nervous system, and may be related to the quantity of toxin released. The period of onset is the time between the first symptom and the start of spasms. These periods are important.
prognostically, the shorter the incubation period or period of onset the more severe the disease.

Clinical manifestations

The diagnosis of tetanus is made on clinical suspicion. The precise manifestation of tetanus is dependent on the parts of the nervous system to which the toxin is transported. Localised (including pure cephalic, from head and ear injuries) and generalised (from spinal cord involvement) are thus described. Localised tetany of the vocal cords has been reported, leading to life-threatening laryngospasm. Generalised tetanus usually presents initially with jaw and neck signs, before spasms and rigidity begin to spread, to affect all muscle groups. Opisthotonus – severe hyperextension and spasticity, causing the head, neck and back to form an arch or ‘bridging’ posture - is a classical manifestation of tetanus. This can be induced by minor stimuli, is extremely painful and can lead to laryngeal obstruction causing asphyxia.

Q. Tetanus can be life-threatening even if localised. Can you explain why?

A. Cephalic tetanus is a rare form of local tetanus that follows head or facial trauma, or ear infection. The incubation period is a few days, laryngospasm is a feared complication explaining high mortality.

Autonomic instability

The leading cause of death in developed world from tetanus is autonomic instability which manifests as labile periods of tachycardia and hypertension, followed by hypotension and bradycardias, leading to cardiac arrest. Non-cardiac manifestations are common, and include ileus, diarrhoea, salivation and increased bronchial secretions and pyrexias.

Specific therapies

Three goals exist: control of toxin, treating spasms and haemodynamic instability. There is a lack of evidence-based literature, and the majority of treatments are based on case reports.

Toxin control

Clostridium tetani is an anaerobic organism and exposure of the wound +/- debridement will minimise the anaerobic environment. Metronidazole is the antibiotic of choice. Intravenous immunoglobulin is of use in treating systemic toxin, and there is emerging evidence that the intrathecal route may be better. Unfortunately, this does not treat toxin already present within neuronal tissue. Supportive care is needed until recovery, which may take up to 4-6 weeks.

Management of muscle spasm

General anaesthetics (including volatile agents) relieve the muscle spasm by increasing activity of inhibitory postsynaptic receptors. Baclofen has been reported to be of use, but when used intrathecally carries a risk of respiratory failure. Maintaining serum magnesium concentrations at 2-4 mmol/L reduces muscle spasm and cardiovascular instability. While the response to depolarising and non-
depolarising agents is no different from normal patients, case reports exist of hyperkalaemic cardiac arrest following succinylcholine use in established tetanus. Deep sedation and occasional neuromuscular blockade is often needed, which may also address issues with haemodynamic instability.

Q. Explain why magnesium administration may reduce the requirement for other drugs to control muscle spasms and cardiovascular instability in tetanus.

A. Magnesium is a cofactor in vital enzymatic reactions, including glycolysis, the Krebs cycle and the respiratory chain, which represent the core of energy metabolism. It also antagonises calcium through calcium channel blocking properties at the level of smooth and skeletal muscle, and conduction system. As such, magnesium induces muscle relaxation, which may control spasms, and cardiovascular effects such as vasodilatation, and reduction of heart rate (not in healthy people), and of systemic catecholamine release, which may improve the effects of autonomic dysfunction.

Managing haemodynamic instability

Unfortunately ‘autonomic storms’ occur without precipitants. Both norepinephrine and epinephrine can be released (the latter to levels associated with phaeochromocytoma), as can acetylcholine, with para-sympathetic effects. Alterations in systemic vascular resistance cause fluctuating systemic blood pressure. Case reports exist of successful use of epidural and spinal bupivicane to control refractory autonomic storms, but with vasopressor support.

Similarly, successful treatments of resistant haemodynamic instability using continuous atropine infusions have been described.


A single gram of toxin, evenly dispersed and inhaled, has the potential to kill more than 1 million people. In current times, this should perhaps not be considered an unlikely but perhaps a possible situation.

**Myasthenia Gravis**

Myasthenia gravis (MG) is an autoimmune disease, most commonly caused by pathogenic antibodies directed at the acetylcholine receptor (AChR), and (sometimes) muscle specific tyrosine kinase receptors. Modification of the synaptic cleft is postulated to damage the postsynaptic neuromuscular membrane. Receptor blockade and destruction result, reducing the number of receptors available for ACh to bind to and increasing the threshold for a muscle action potential.

Muscle weakness and fatigability result. Ocular symptoms are near-universal, often appear early and can indeed be the sole feature. Limb weakness is common, and is worse after exertion. Bulbar involvement may lead to difficulty in speaking and swallowing. Weakness of laryngeal muscles is associated with a hoarse, breathy voice. Incomplete glottic closure during swallowing may lead to aspiration. Respiratory fatigue leads to dyspnoea and ultimately ventilatory failure. Treatment is with tailored doses of anticholinesterase drugs. In the United States, while rare (annual incidence 0.01/1000 persons/year), it carries a mortality of 2.2% (and 4.7% in myasthenic crises - see below).

- **Anticholinesterases may increase respiratory secretions in intubated patients and delay weaning.**

- **Caution must be exercised in the use of competitive NMBAs in patients with myasthenia gravis - their duration of action may be greatly prolonged. Short-acting non-depolarising agents are preferred.**

Further reading:


**Common presentations**

Patients with Myasthenia often present in respiratory failure after surgery. This may be due to cessation of anticholinergics or directly as a result of thymectomy (see below). Other presentations include myasthenic crises, with a rapid deterioration in...
muscle strength. Respiratory failure may also occur in previously-undiagnosed patients, and in those receiving inadequate doses of anticholinesterase medications.

Patients may present in respiratory failure requiring mechanical ventilation. It is important to underline that - contrary to GBS, where a steady decrease of ventilatory capacity is generally observed, thereby rendering ventilatory tests such as FVC reliable in predicting the need for ventilatory support - the reduction of ventilatory performances can be sudden and may be very variable in MG. Therefore, ventilatory tests such as the FVC are not reliable in predicting the need for ventilatory support in patients with MG.

Other than after surgery, infection, trauma or the post-partum state may cause an acute deterioration/myasthenic crisis and precipitate ICU admission.

Several drugs commonly used in the ICU may also aggravate the muscle weakness or, rarely, unmask a previously-undiagnosed myasthenia gravis. These include non-depolarising NMBA, antibiotics (aminoglycosides, polymixin B, clindamycin), drugs with neuromuscular blocking-like action (lidocaine, procainamide, quinidine, phenytoin), calcium channel blockers, magnesium, beta blockers (especially propranolol), diuretics (via loss of electrolytes) and quinolones.

Overtreatment with anticholinesterases can lead to cholinergic crises. Weakness and ventilatory failure occur, with increased salivation, abdominal colic, diarrhoea, sweating and small pupils.

**Immediate measures**

The diagnosis and treatment need, as in most acute medical situations, to evolve concurrently.

Priorities in the myasthenic patient with respiratory failure are:

- Rapid assessment of the need for respiratory support
- Increase in anticholinesterase drugs
- Corticosteroid introduction/increase (which may or may not aid acute recovery, but will aid longer term muscle strength)
- In cases which do not respond to anticholinesterases and corticosteroids, plasma exchange or intravenous immunoglobulin have both been shown to be efficacious.

If the weakness and ventilatory failure is due to overtreatment with anticholinesterases, the treatment is to withdraw drug therapy for at least 24 hours, maintain monitoring and supportive measures, and to reintroduce drugs at a lower dose.

If NMBA agents are suspected as the cause of weakness and ventilatory failure - particularly in the postoperative phase - sugammadex, particularly in the case of rocuronium use (or less specifically when other steroid NMBA have been used), may be used to reverse NMBA effect.

Further reading:
Specific ventilation issues

A single study has attempted to use non-invasive ventilation to prevent intubation.

Weaning should begin only once plasmapheresis or intravenous immunoglobulin has been given, and the patient shows signs of improvements in vital capacity/ negative inspiratory force generation. Extubation failure is common (44%) and the presence of atelectasis the best predictor. The mean ventilation time in a recent series of ventilated patients was two weeks.

Further reading:


Diagnosis

Diagnosis of MG is confirmed by the presence of acetylcholine receptor antibodies, which are specific for this disease, although not found in all cases. Anti-striated muscle antibody is also positive in some patients, particularly those with a thymoma, but is not specific.

Edrophonium challenge: This should only be performed in patients with obvious ocular signs - a positive test is subjectively determined by an improvement in clinical signs. Edrophonium prolongs the action of acetylcholine at the receptors, augmenting strength in affected muscles. However it potentiates the muscarinic effects too - ischaemic heart disease and asthma are therefore relative contraindications.

Edrophonium must be administered in an area where full resuscitation facilities are available because of the potential for cardiovascular collapse. Given the risks of edrophonium challenge, this test is not performed routinely and should only be used when the diagnosis of MG is unclear.

Electrophysiology: Repetitive nerve stimulation displaying a 10% decrement in compound muscle potential is used to demonstrate the neuromuscular transmission defect. Single-fibre electromyography can be useful in the patient with suspected myasthenia gravis in whom results of other tests of neuromuscular transmission and acetylcholine receptor antibody measurements are normal.
Specific treatment

Other than the treatments outlined under ‘Immediate measures’ above, there will be the management of the patients admitted postoperatively which will fall into two categories:

- Post thymectomy
- After other surgical procedures.

Thymectomy is usually considered if other treatments have failed to control the disease, but early thymectomy can be offered in young (<45 years) AChR-positive patients. Postoperatively, controlled ventilation is usually required for at least 24-48 hours. Anticholinesterase therapy should be withheld in these patients and then reintroduced in a lower dose after about 24 hours. Clinical assessment and spirometry are a guide to therapy.

In patients undergoing non-thymoma surgery, anticholinergic drugs should be withheld six hours before surgery and reinstated with caution postoperatively as sensitivity may have changed. Another concern is that these drugs may facilitate leakage from new bowel anastomoses.

For further reading:


Motor neurone disease

Motor neuron disease is caused by a primary degeneration of the anterior horn cell followed by distal axonal degeneration. The most common form, Amyotrophic Lateral Sclerosis (ALS), is a progressive, and ultimately fatal, degenerative neurological disorder. It presents with both upper and lower motor neuron signs, generally in patients aged 50-60 years. Most present with limb weakness or bulbar symptoms but may rarely present in ICU as a failure to wean associated with a separate (apparently unassociated) pathology e.g. postoperatively or post COPD exacerbation.

The clinical features are of weakness and wasting with muscle fasciculation. Tendon reflexes are brisk, and plantar responses extensor. Cough and gag reflexes are reduced, and the tongue wasted with fasciculation. Acute respiratory failure universally complicates the course of the disease, either because impaired clearing of secretions facilitates aspiration pneumonia or respiratory muscles fail to maintain adequate ventilation (neuromuscular respiratory failure). There is no specific test for amyotrophic lateral sclerosis. The clinical features and exclusion of other
diseases has to suffice. Internationally accepted criteria are:
1. Presence of lower motor neurone degeneration defined clinically, neuropathologically or on electrophysiology.
3. Progressive spread of symptoms and signs, from history or examination.


Non-invasive ventilation improves quality of life, and probably prolongs it. Criteria for initiation of non-invasive ventilation are:
1. Vital capacity <50% predicted
2. Sniff nasal pressures of <40 cm
3. Orthopnoea
4. Abnormal nocturnal oximetry.

At the stage where invasive ventilation is required in the absence of reversible causes, recovery to pre-morbid conditions is rare. Careful, early, multi-specialty coordination of discussions on end-of-life care are necessary to prevent patient and family distress.

Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. Arch Neurol 2010; 67(9): 1089-1094. PMID 20837853


Myotonic dystrophy

Myotonic dystrophy is a chronic slowly progressive disease affecting multiple systems, being associated with muscle wasting and slow relaxation of contracted muscle (myotonia) and also with cardiac conduction abnormalities, cataracts, and even hormonal changes. It may be hard to diagnose because clinical features can initially be subtle.

The need for intensive care can be precipitated by cardiac arrhythmias or by respiratory muscle weakness. Patients may have very prolonged respiratory
depression after anaesthesia even for minor surgery, presenting as ‘difficulty in reversing NMBAs’ or failure to breathe adequately postoperatively. Cardiac failure secondary to poor left ventricular function (common in myotonic dystrophy) can exacerbate this.

If respiratory failure occurs without an easily reversible precipitant, the prognosis is poor. Home non-invasive ventilation is useful in buying time in the face of respiratory failure in patients with muscular dystrophies.

**Rhabdomyolysis**

Rhabdomyolysis is a syndrome of skeletal muscle breakdown with leakage of muscle components into the systemic circulation. It is not uncommon and causes include:

- Drug- (propofol, statins, fibrates) or toxin- (cocaïne, heroin) induced rhabdomyolysis
- Ischaemic rhabdomyolysis induced by prolonged recumbency (compression)
- Exertional rhabdomyolysis
- Trauma
- Rapidly progressive inflammatory myopathy
- Metabolic and electrolyte disorders
- Hyper- or hypothermia-induced rhabdomyolysis
- Infection-induced rhabdomyolysis.

For further information about the causes of rhabdomyolysis, see:


**Clinical features**

Rhabdomyolysis leads to leakage of muscle cell contents, including myoglobin potassium, and muscle enzymes including creatine kinase, all of which levels may be used in diagnosis. Myoglobin is usually detected (indirectly) on urinary dipstick testing which shows a positive result for blood even when there are no red cells in the sediment; if myoglobinuria is gross, the urine appears dark, opaque, and tea-coloured.

Clinical features depend upon the cause and pattern, but may include rapid onset of severe muscle pain, stiffness, tenderness and limb weakness. Electrophysiological and muscle biopsy findings are usually normal which is consistent with rapid and complete muscle recovery; however when there is massive leakage of muscle content, this may result in hyperacute hyperkalaemia (causing cardiac arrest) and also damage to distant organs (multi-organ dysfunction).
Specific therapy

The cause should be addressed and corrected whenever possible. Corticosteroid and immunosuppressive therapy may be required for inflammatory myopathies. Fasciotomy may be necessary for compartment syndrome. Occasionally, extensive debridement is required to prevent gross muscle damage. Hypocalcaemia is a common complication of rhabdomyolysis, resulting from calcium entering the damaged muscle cells and from the precipitation of calcium phosphate with calcification in necrotic muscle. Correction of hypocalcaemia should be considered only if symptomatic (e.g. tetany or seizures) or if severe hyperkalaemia occurs.

In addition, patients will lose large amounts of intravascular fluid into the damaged muscle and other soft tissues and close attention must therefore be given to restoring circulating volume and blood pressure.

Regardless of aetiology, severe rhabdomyolysis triggers a pathogenetic cascade, of which myoglobin plays a dominant role, potentially leading to acute renal failure. Urinary alkalinisation may reduce formation of myoglobin and urate crystals (which is promoted by a low urine pH) but clinical efficacy has not been established. Haemodialysis or continuous haemofiltration can be necessary if an adequate urine flow cannot be established.

Q. Explain why muscle damage can lead to acute kidney failure.

A. Rhabdomyolysis may lead to substantial release of myoglobin from muscle into the circulation. Although this myoglobin is soluble in an alkaline, dilute urine, it may precipitate out into the renal tubules and lead to kidney failure when a patient is dehydrated and acidotic.

Q. What measure would you institute in order to minimise the risk of renal failure in a patient with rhabdomyolysis?

A. The most important measure is to restore circulating volume and blood pressure as soon as possible. Alkalinisation of urine may help to prevent deposition of myoglobin in the renal tubules but clinical efficacy has not been demonstrated.

See the PACT module on Oliguria and anuria (AKI part I).

Hypercalcaemia is unique to the late recovery phase of acute renal failure induced by rhabdomyolysis, and results from the mobilisation of calcium that was previously deposited in muscle, the normalisation of hyperphosphataemia, and an increase in the active form of vitamin D.

For further information about acute renal failure in rhabdomyolysis:

Drugs and toxins

Organophosphates

These inactivate cholinesterase, producing a variety of clinical signs and symptoms. Muscarinic effects include blurred vision, sweating, hypotension, dyspnoea, cough, wheeze, vomiting and diarrhoea. Nicotinic effects include muscle fasciculation, weakness and paralysis. These effects usually occur within 12 hours of exposure, and mechanical ventilation may be required.

See the PACT module on Environmental hazards.

Statin therapy

While myalgia is relatively common with statin therapy, myopathy itself is only seen in 1% of these patients. Life-threatening rhabdomyolysis and myopathy occurs only secondary to drug interactions - most commonly with macrolide antibiotics.

Serotonin syndrome and amphetamines

The use of recreational drugs can lead to hyperthermia (e.g. ecstasy via serotonin syndrome, amphetamines via its stimulant effects) which may be associated with Disseminated Intravascular Coagulation and rhabdomyolysis. Treatment includes cooling and the use of benzodiazepines to ameliorate the central response.

THINK Some neuromuscular disorders may be present before ICU admission, but may not have been diagnosed. Where weakness occurs in the ICU, it is sensible to look for evidence of pre-existing neuromuscular problems before assuming that weakness is due to post-ICU problems.
A 73-year-old female was initially admitted to the ICU because of acute pancreatitis caused by gallstones and a pancreatic pseudocyst complicated by pneumonia and sepsis. After the acute inflammatory state resolved, she was discharged to a rehabilitation centre with normal limb and respiratory muscle strength. Two weeks later she developed bilateral lower limb paresthesias followed by bilateral progressive leg weakness and difficulty in walking. Guillain-Barré syndrome was suspected, and diagnosis was confirmed by electrophysiological investigations. Cerebrospinal fluid also revealed increased protein with normal white blood cell count, and hence an intravenous immunoglobulin G infusion was started and she was re-referred to ICU. Within 48 hours, she progressed to complete flaccid tetraparesis with involvement of respiratory muscles requiring mechanical ventilation. While in the ICU, she developed severe autonomic disturbances, pneumonia, sepsis, and multiple organ failure leading to death. As this case teaches us, GBS must be always suspected if neurological signs and symptoms start several days to weeks after the resolution of an infection or acute inflammatory process.

A 30-year-old male was admitted to the ICU from the emergency department following a respiratory arrest. Friends reported that he had, that day, attended the out-patient department of another hospital. The next day he improved, and no longer required ventilatory support. He deteriorated over the next few hours, and mechanical ventilation had to be reinstituted. Again he improved over 24 hours, and was able to write (while still intubated and ventilated) that he wished firstly to have his endotracheal tube removed, and secondly to continue the investigations he had been having for a lump in his chest at the other hospital! He had undiagnosed myasthenia gravis. The lump in his chest was eventually proved to be a thymoma.
Often diagnosed during ventilator weaning, neuromuscular weakness increases ventilator-, ICU- and hospital-days, is associated with post-discharge morbidity, and is an independent predictor of mortality. Causes can be categorised as follows:

1. Intensive Care Unit-Acquired Weakness (ICU-AW)
2. Prolonged neuromuscular blockade
3. Metabolite and electrolyte disorders
4. Rare and related conditions.

**Intensive Care Unit-Acquired Weakness (ICU-AW)**

ICU-AW, first recognised in 1977, is an encompassing functional description of post-critical-illness weakness of all causes, once primary neuromuscular diseases detailed above have been excluded. It affects 25-50% of critically ill patients at awakening and may be primarily neuropathic, or myopathic in origin, or the result of both.

Critical Illness Myopathy (CIM) refers to a muscle-predominant form and Critical Illness Polyneuropathy (CIP) to weakness which results from axonal neuropathy. ‘Critical Illness Neuromyopathy’ (CINM) refers to the co-existence of both.

Separating these elements is not always easy, and the value of electrophysiological study is debated. Such tests can be technically challenging (due to sedation, paralysis and oedema), may reveal early and near-universal abnormalities which do not predict later weakness or neuropathy, and don’t readily differentiate CIM and CIP in the sedated patient. Further, separating CIP, CIM and CINM as different syndromes usually confers no clinical value if other diseases have been excluded.

Diagnosis is thus usually made through exclusion of other disease states, and on clinical grounds. If intrinsic muscle pathology cannot be excluded, a muscle biopsy may be indicated. The term ICU-acquired weakness (ICU-AW) designates clinically detected weakness in critically ill patients in whom there is no plausible aetiology other than critical illness.

**THINK** Weakness may be so profound that a lack of motor response to painful stimuli leads to an erroneous conclusion that the patient has suffered brain damage. In some cases a grimace may be the only motor response from the patient.

ICU-AW should be considered in all patients with a likely precipitant (e.g. sepsis, multi-organ failure), who have a generalised weakness, decreased muscle tone, normal reflexes (though they can be increased or absent), with sparing of the cranial nerves. The best current test is the Medical Research Council Sum Score (MRC-SS, see figure in Task 1), a score of <48 (an arbitrary definition) labelling a patient as ‘weak’ with increased risk of associated complications. This is an imperfect system, as over 30% of ICU patients are unable to perform testing at awakening, and inter-rater reliability is suboptimal. Proximal muscle wasting is also common and of initial substantial functional importance, but is underrepresented in the MRC-SS.
Critical illness polyneuropathy (CIP) indicates patients with ICU-AW who have electrophysiological evidence of an axonal sensory-motor polyneuropathy, and critical illness myopathy (CIM) indicates patients with ICU-AW who have electrophysiologically and/or histologically defined myopathy.

**NOTE** CIP and CIM are most often combined, a condition defined as critical illness neuromyopathy (CINM).

CIP and CIM are complications arising after the onset of critical illness, usually after admission to the ICU. In CIP, limb and respiratory muscles are affected, whereas facial muscles are spared. Limb involvement is symmetrical, it is most prominent in the lower extremities and can be severe enough to cause paralysis. CIM is a primary myopathy, whose clinical features are often much the same as for CIP, but, if testable, there is normal sensation.

**THINK** Remember that there are many other causes of difficulty in weaning. Pay close attention to cardiovascular function, respiratory mechanics and abdominal complications before assuming weaning is delayed by CIP or CIM.

**THINK** Remember that CIP and CIM most often coexist.

*Clinical relevance*

Patients with ICU-AW have respiratory muscle weakness, more ventilator-dependent days (18 days versus seven days), and greater ICU and hospital stays and mortalities. Reduced functional capacity (using six minute walk test) at one year persistent for five years or more has been demonstrated in many survivors who describe muscle weakness as the primary cause. As a result, over half of patients of a working age do not return to work at one year, and a third require assistance with activities of daily living. Persistent entrapment neuropathies and foot drop have also been reported.

**ANECDOTE** An 18-year-old man was admitted to the ICU because of chest trauma complicated by ARDS, severe sepsis and MOF requiring prolonged use of sedatives and NMBAs. After the acute condition resolved, and pulmonary infiltrates on chest X-ray cleared, the sedation was stopped and patient was allowed to awaken. Cognition was intact, but the patient was unable to breathe spontaneously. Clinical evaluation showed severe muscle wasting and weakness in all four limbs. Nerve conduction studies demonstrated CIP. Tracheostomy was performed, and the patient was transferred to a respiratory care unit where he was eventually weaned from the ventilator two months later. Recovery of lower limb muscle strength required six more months of active physical therapy in a rehabilitation centre.

**Interventions**

Passive stretching preserves muscle architecture in the sedated paralyzed patient, but does not preserve protein content (resistance exercise being required to build muscle). No treatment is proven to prevent muscle wasting in these patients, although minimising the use of sedation, with an integrated early mobilisation
programme may reduce ventilator dependency and ICU length of stay, and improve functional outcome. The role of nutrition (as regards timing, mode and composition) in preventing muscle wasting is unclear. Intensive insulin therapy reduces electrophysiologically-proven CIP, but increases the risk of hypoglycaemia and, if aiming at normoglycaemia, increases mortality and cannot be recommended.

**NOTE** Muscle biopsy is not indicated in the acute stage of critical illness. At a later stage, if muscle weakness persists, muscle biopsy may offer clues to prognosis.

**NOTE** Discuss with experts of neuromuscular disorders in your hospital if needle biopsy of muscle can be done under local anaesthesia in the ICU. Results can be equally as informative as those from an open biopsy.

**NOTE** Intensive insulin treatment has been shown to reduce the occurrence electrophysiologically-proven CIP. Evidence that it can also reduce ICU-acquired muscle weakness is lacking.

*Rehabilitation in the community*

There are currently insufficient data to be able to advise on the most effective strategy to aid rehabilitation in the community.

**Q.** There are many causes of delayed weaning from mechanical ventilation. What, on clinical observation, would make you suspect CIP or CIM specifically?

**A.** The usual features raising a suspicion of CIP, CIM (or CINM) would be the absence, or substantial reduction, of spontaneous limb movement, the patient’s dependence on the ventilator and the sparing of the facial nerves (patients often grimace to pain) arising *after* ICU admission.

**Q.** What might you find on physical examination of the patient?

**A.** This is likely to reveal absent or grossly diminished reflexes (presence of normal reflexes does not rule out the diagnosis). In patients with pure CIM, sensation is intact.

**Q.** Would you interrupt administration of steroids in a patient with CIM?

**A.** This is a difficult question to answer, because steroids have been described as a risk factor for CIM in some studies, but not in others. In one study, steroids were even found to be an independent protective factor for the occurrence of CIP/CIM.

**Q.** In patients in whom steroids may be needed as a chronic treatment to control inflammatory or autoimmune diseases, would you stop or maintain the steroid therapy?

**A.** In such cases, steroids can be maintained unless monitoring of serum CK indicates a rapidly progressing muscle necrosis.
Q. In patients with septic shock, in whom steroids can reduce the weaning time from vasoconstrictors (but with no proven beneficial effect on mortality), would you stop the steroid?

A. The evidence is swinging towards stopping (or earlier cessation of steroid in this situation) as recent evidence from the Surviving Sepsis Campaign database suggests that steroid use is associated with increased hospital mortality.

Q. What would you do to ensure the safe discharge of a patient with CIP from the ICU?

A. This requires great planning, which is often difficult to achieve. The most important life-threatening problems after discharge are difficulty in coughing, swallowing and mobilising.

Further reading:


**Prolonged neuromuscular blockade**

Confusion exists in the minds of some between neuromuscular *paralysis* and neuromuscular *weakness*. Most neuromuscular blocking agents (NMBAs) are excreted via the liver and/or kidneys, and their accumulation (or that of their active metabolites) can prolong *paralysis*. Constant patient surveillance is needed, dosage should be minimised, and regular ‘paralysis holds’ performed. Monitoring by peripheral nerve stimulation (Train-of-Four response) is preferable.

See Train-of-Four testing in Task 4 (monitoring neuromuscular blockers) of the PACT module on Sedation and Analgesia.

While prolonged paralysis may occur, the use of NMBAs is not proven to play a causative role in ICU-AW pathogenesis. In the only randomised control trial of NMBAs in ARDS, no difference in ICU-AW incidence was seen between groups.
Q. In what way might critical illness influence the metabolism of NMBAs?

A. The major routes of elimination of NMBAs are the liver and kidneys. Dysfunction (not necessarily failure) of these organs may lead to accumulation of NMBAs or their metabolites. Endocrine and metabolic dysfunction may also lead to delayed metabolism of these agents.

**NOTE** Remember that suxamethonium (succinylcholine), a competitive NMA providing rapid onset neuromuscular blockade, may lead to sudden increase in plasma potassium in patients with myopathy either ICU-acquired or pre-existing.

You may wish to discuss with the consultant anaesthetists of your hospital about the use of competitive non-depolarising NMBAs in patients with myasthenia gravis. Sugammadex is a selective binding agent that may fully reverse even profound neuromuscular transmission block induced by the steroidal NMDA, rocuronium and thereby may prevent residual neuromuscular blockade in this situation.

For further information please see:


**Metabolic and electrolyte disorders**

High and low levels of sodium, potassium, magnesium, calcium and phosphate are common in ICU, either as part of the presenting acute disease, or as complications of physician initiated therapy. Hypophosphataemia specifically can be a side-effect of refeeding syndrome. Correcting the underlying cause and replacing electrolytes will ameliorate symptoms. This approach is also of use in hypothyroidism and hypoadrenalism, both of which may cause muscle weakness.

Please see the PACT module on Electrolytes and Homeostasis.
Other Critical Care related complications

**Delirium** is an acute, fluctuating change in consciousness and cognition that frequently develops in critically ill patients, particularly those on mechanical ventilation. Delirium and muscle weakness are both influenced by severity of critical illness and immobility, and interact with each other.

**Q. Comprehensive physical and occupational rehabilitation can improve both muscle strength and mentation. Can you explain why?**

**A.** ICU-acquired muscle weakness and delirium potentiate each other. Therefore, rehabilitation should target both the body, through physical therapy, and the mind through occupational therapy.

**Propofol infusion syndrome (PRIS)** is a rare syndrome of cardiac failure, severe metabolic acidosis, rhabdomyolysis, renal failure, and hypertriglyceridaemia caused by prolonged infusion of high-dose propofol. However, the syndrome can occur with short-term use of propofol. Individual components of the syndrome are frequently recorded. The incidence of propofol infusion syndrome is high in patients with severe head trauma or acute inflammatory syndromes.

The pathophysiology of PRIS is complex (see also the PACT module on Sedation and Analgesia). If you want to know more on PRIS pathophysiology and incidence, read the following references:


**ANECDOYE** A 58-year-old woman recovering after severe abdominal trauma complicated by peritonitis, sepsis and MOF was assessed after ICU discharge for suspected neuromuscular respiratory failure. When required, she was unable to count to 20 with a single breath. Coughing and clearance of secretions were impaired. The patient was able to lift her arms and legs, but not against resistance. Nerve conduction study and electromyography documented combined CIP and CIM. A ten-day aggressive chest physiotherapy achieved respiratory muscle recovery with normalisation of clinical symptomatology and of FVC, MIP and MEP.
Neuromuscular disease within the ICU is broadly split between primary conditions causing admission, and weakness which results from critical illness. Prompt recognition of and treatment of the conditions causing weakness, and management of its consequences, can decrease morbidity and also may reduce mortality.
Patient 1

You are called to see a 30-year-old male patient in the operating theatre recovery area because he has failed to re-establish normal respiration postoperatively. The patient’s risk categorisation was low when seen pre-operatively (graded ASA I). The operation was an uneventful hernia repair performed under general anaesthesia. Since the patient is making no respiratory effort you arrange for transfer to the ICU while he remains intubated and ventilated.

Causes of postoperative weakness

The causes of postoperative weakness are considered under four headings:

1. Surgical reasons
2. Anaesthetic factors
3. Perioperative complications that might be causative
4. Background factors which might account for the weakness.

In light of the above, outline your clinical analysis, in this patient, of the most likely cause for his weakness and respiratory failure? Please consider them under these four headings:

Q. Surgical factors?
A. In the context of a lower abdominal procedure, it is most unlikely that surgical factors play a role here. It is conceivable that with major gastric or oesophageal surgery, or with thoracic surgery that there may be a failure to breathe.

Q. Anaesthetic factors?
A. It is possible that anaesthetic factors play a role. In the elderly or infirm there may be undue sensitivity to anaesthetic agents, but in a young, fit man this is unlikely. It could be important however to look for possibilities such as excessive or miscalculated doses of volatile agents. In addition the doses of competitive neuromuscular blocking agents (NMBAs) used, if any, should be scrutinised. It would be important to determine whether suxamethonium (succinylcholine), a non-competitive neuromuscular blocking agent used for rapid tracheal intubation, had been administered as in the event of pseudocholinesterase deficiency, this may cause an abnormally long duration of action of the agent.
Q. Intra-operative events?
A. It is possible but unlikely that the patient has suffered an intra-operative catastrophe such as a cerebral or myocardial infarction.

Q. Pre-existing disease?
A. Pre-existing neuromuscular conditions, which may never have been diagnosed, including some of the muscular dystrophies, myasthenia gravis and neuropathies may present in this manner.

When you admit the patient to the ICU, you note that the train-of-four stimulus testing, which was done in the postoperative recovery area, was normal.

Learning Issues

Train-of-four neuromuscular testing in the diagnosis of postoperative weakness

The patient regains consciousness, but not the ability to breathe spontaneously nor to move his limbs. Sensation is intact. Your colleague points out that the absence of sensory abnormalities indicates that function is likely altered at the level of neuromuscular transmission or at the muscle itself. You add that the normal train-of-four testing excludes an abnormality of neuromuscular transmission.

The electrocardiogram (ECG) reveals infrequent ventricular ectopic beats and a ten-second episode of complete heart block. The patient's family is called in urgently and they ask to speak to you. You notice that the father has a firm handshake and slurred speech. He wears thick lensed 'pebble' glasses.

Q. What do you think the diagnosis is?

PROMPT: The firm handshake may reflect difficulties in relaxing grip. The visual impairment may be compatible with the early cataract formation.

A. The combination of features, both in the patient and seen in the father, suggests a diagnosis of myotonic dystrophy.
Muscular dystrophies causing respiratory failure

The patient is successfully weaned from respiratory support over the next three days. As the patient is suspected of having an autosomal dominant disease you advise referral to Neurology and to a centre for genetic counselling.
Patient 2

A 43-year-old female presents to her family doctor with symptoms of a mild upper respiratory tract infection and he prescribes a course of antibiotics. Two days later, she develops diarrhoea. Her symptoms resolve over the next four days, but one week later she notices cramp in her calves. When she starts tripping over furniture in her house, she attends her local hospital. No abnormalities are detected and she is discharged home with a diagnosis of hysteria. The next day she cannot get out of a chair and returns to the hospital. She refuses to go home, and is admitted to a medical ward. Later that day you are called to see her because she is complaining of difficulty breathing. A junior member of the medical team reports that her blood gases are normal, and he asks if this could be Guillain-Barré syndrome (GBS). She has no sensory signs.

Learning Issues

Pathophysiology of Guillain-Barré syndrome (GBS)

Blood gases in GBS and other weakness syndromes

Q. What are the arguments for a diagnosis of GBS?

A. This is a classic presentation of GBS. The acute presentation in someone previously well precludes most other causes of weakness.

Q. What are the other most likely causes?

A. An alternative explanation includes hypokalaemia given the history of diarrhoea. The myopathies associated with endocrine disorders should be considered, as should myasthenia gravis.

NOTE Guillain-Barré syndrome is often missed in the early stages, when the clinical signs may be inconclusive.

Learning Issues

Myasthenia gravis

After assessment, you admit the patient to the ICU for airway protection and ventilatory support and for further investigations.
Q. What is the broad approach to management?

PROMPT: Remember that there will be both specific and supportive therapy

A. There are two priorities. The first is to assess and support respiratory function, and the second is to make a diagnosis thus facilitating specific therapy.

In terms of the supportive management, it cannot be overemphasised that blood gases in most patients with acute weakness are usually normal until the time of the respiratory arrest and are therefore useless as a guide to impending respiratory failure. The patient is best monitored with serial Forced Vital Capacity (FVC) measurements. If the absolute value of FVC is <1 L or <20 mL/kg, or is rapidly declining in subsequent measurements, mechanical ventilation should be considered.

Maximal inspiratory (MIP) and expiratory pressures (MEP) would also be insightful. MIP of <30 cmH₂O or MEP of <40 cmH₂O would also predict impending acute respiratory failure.

GBS may also be associated with difficulties in coughing or swallowing, and therefore any clinical suspicion of aspiration should lead to protection of the airway either by tracheal intubation or tracheostomy - usually by tracheal intubation in the first instance.

Learning Issues

Clinical evaluation of GBS level of disability

Forced vital capacity (FVC) testing in GBS

Q. Which tests would you do to make the diagnosis of GBS?

A. CSF for elevated cerebrospinal fluid protein after the first week of the disease.

Nerve conduction testing for:
Slowed nerve conduction velocity
Reduced compound muscle action potential

Q. What are the specific therapies for GBS and how are they delivered?

A. The specific treatments of GBS consist of immunoglobulin by IV infusion or plasma exchange - usually via a dialysis catheter.
Q. Do these treatments influence the Critical Care course?
A. Either of these therapies reduces time spent on mechanical ventilation and promotes faster recovery of mobility.

**Learning Issues**

Airway support and ventilation

Treatment of Guillain-Barré syndrome

The patient's husband wants to talk to you. He is very concerned but also angry that the hospital initially misdiagnosed his wife's illness and sent her home.

Q. What do you say to him regarding her clinical course to date and its implications for her recovery?
A. You express regret that his wife was initially considered hysterical. You, however, explain that in the beginning of this disease, symptoms are typically vague and normally progress slowly. In his wife's case, however, the onset has been rapid.

Q. He asks if the rapid progression has implications for the ongoing evolution of the disease.
A. You explain that, unfortunately, this is usually associated with a poorer physical recovery.

Q. He then enquires about the nature of the hospitalisation required and the likely long-term outcome.
A. Although traditionally it had been held that all GBS patients make a good neurological recovery, it is now known that up to 20% of patients will have residual motor dysfunction in the long term, and will require ventilatory support early in the course of their illness.
Patient 3

A 68-year-old female is admitted to the ICU after emergency surgery for a perforated colonic diverticulum. There was gross faecal contamination of the peritoneal cavity at laparotomy. On admission to the ICU, she is receiving mechanical ventilation facilitated by infusions of morphine and midazolam. The vecuronium infusion, which was commenced in the operating theatre, is discontinued. Over the next 24 hours she develops evidence of severe sepsis, requiring circulatory support with norepinephrine. Despite maintenance of adequate cardiac output and blood pressure, renal dysfunction develops requiring continuous venovenous haemodiafiltration. Continuing high volume gastric aspirates necessitate parenteral nutrition.

See the PACT module on Nutrition.

After two weeks, the cardiovascular failure has resolved and gas exchange has improved to near normal. A decision to reduce sedation to facilitate weaning from mechanical ventilatory support is made. Twenty-four hours later she opens her eyes spontaneously but makes minimal respiratory effort. There is no response to painful stimuli other than grimace. Reflexes are diminished, and the plantar response is normal.

Learning Issues

Assessment after long ICU stay

Q. What are the most likely causes of her weakness?

A. You consider the following the most likely diagnoses:

Weakness following long-term sedation due to metabolites from midazolam and/or morphine

Critical illness polyneuropathy (CIP)

Learning Issues

Critical illness polyneuropathy

See the PACT module on Sedation and Analgesia
Q. What investigations would you order?

A. You suspect critical illness polyneuropathy (CIP) and order electrophysiological studies to confirm the diagnosis. This may reveal evidence of neuropathy or myopathy.

**NOTE** Investigations are not always necessary – remember to use your clinical skills!

CIP is a frequent complication of prolonged critical illness; in the appropriate clinical context and in the presence of characteristic clinical features, diagnosis is almost certain. Further investigations may be required if weakness persists despite rehabilitation.

Q. What treatment do you initiate?

A. There is no specific treatment. Supportive treatment includes respiratory support until respiratory muscle strength improves and weaning criteria are met. Other standard supportive care includes the maintenance of thromboembolism prophylaxis.

See the PACT modules on Respiratory assessment and monitoring and Mechanical ventilation

**Learning Issues**

Treatment of critical illness polyneuropathy

Two weeks later, the patient’s tracheal tube becomes obstructed, and is rapidly changed after administration of etomidate and suxamethonium (succinylcholine). Two minutes later the patient suffers a cardiac arrest.

Q. What is the most probable explanation?

**PROMPT.** Although rare, this is a life-threatening complication. Non-depolarising NMBAs are better suited for use in the ICU.

A. The patient probably suffered a hyperkalaemic cardiac arrest. Muscle has become denervated due to critical illness polyneuropathy, and in these circumstances there is an exaggerated response to a depolarising NMBA (suxamethonium).
The patient is resuscitated successfully. However, ventilatory support has to be continued for another week. Three weeks after the cardiac arrest the patient is extubated but limb weakness still persists, greatly limiting her functional independence in daily activities. The patient wants some more information about speed of recovery of muscle strength.

Q. How can you improve the ability to prognosticate?

A. Electrophysiological investigations of peripheral nerves and muscle may be usefully implemented in cases of persisting muscle weakness and re-referral to the Neurology service may be useful.

Severity of muscle weakness is not correlated with electrophysiological diagnosis, but rapidity and completeness of recovery are. Since CIM has a better prognosis than CIP, You may ask Neurology and the clinical neurophysiologist of your hospital whether it is possible to precisely define the pathological diagnosis. Needle biopsy of muscle can also be proposed at this stage, because some histologic features, such as thick-filament myopathy, are associated with a good prognosis.

Learning Issues

Critical illness polyneuropathy prognosis
Patient 4

A 32-year-old male is admitted having been found acting strangely by the police. On admission to the emergency department, drug intoxication is initially suspected but he quickly suffers a series of grand mal convulsions. He is tracheally intubated and ventilated prior to computed tomography (CT) scan, which shows no abnormality. He has a high temperature of 40°C, is hypertensive (blood pressure 200/140), and showing signs of cerebral irritation. He is admitted to the ICU. He grimaces on muscle palpation and the urine, following catheterisation, is sent for toxicology analysis and is noted to be dark reddish in colour.

**NOTE** Patients do not always present with obvious muscle involvement - you will need to look for it to avoid serious complications later.

Q. What is the most likely diagnosis?

PROMPT: Think about how muscle might be damaged here and why?

A. This is almost certainly drug-induced rhabdomyolysis which may also occur due to (or be exacerbated by) status epilepticus-induced agonist-antagonist muscle contraction. In the context of initial behavioural disturbances followed by a convulsion, hypertension and pyrexia, this may well be due to intoxication. The likeliest agents are cocaine or amphetamines, which induce all of these features.

You measure serum creatine kinase (CK) which was >100 000 U/L and serum potassium and you diagnose rhabdomyolysis. The patient is still unconscious and does not move his legs. Respiratory efforts are somewhat reduced.

**Learning Issues**

Rhabdomyolysis as a cause of weakness (Task 3)

Q. Outline the pathophysiologic process and its immediate life-threatening consequences?

A. Clinical problems arise from muscle content leakage damaging distant organs and from the metabolic consequences of the ‘rhabdomyolysis syndrome’, particularly the associated hyperacute rise in serum potassium.
Q. Presuming the drug toxin aetiology is diagnosed and managed, how would you conduct the supportive management of this patient’s rhabdomyolysis?

A. The standard first priorities are to secure the airway, ensure adequate ventilation and oxygenation and, in the patient described, to prevent further convulsions. Fluid resuscitation is critical to the circulatory management, since this pathology induces oliguria (initially due to hypovolaemia primarily) and an acid urine which are associated with myoglobin deposition in the renal tubules - all risks for acute kidney injury (AKI).

See the PACT module on Oliguria and anuria (AKI part I)

Q. It is stated that recovery of muscle can be rapid and complete if complications are diagnosed in a timely manner and aggressively treated. Outline the muscle-focused monitoring and care involved.

A. Creatine kinase (CK) should be monitored to gauge the amount of muscle damaged, CK activity should decline at about 50% per day unless there is continuing muscle damage or renal dysfunction. Be aware of the possibility that a compartment syndrome may develop and may need muscle (and limb) preserving intervention.

Q. Can urine dipstick testing be useful to the monitoring of myoglobinuria?

A. Yes, indirectly. Presuming there is no haemoglobinuria, the urine may be dipstick tested by utilising the ‘haemoglobin’ measurement as a surrogate marker for myoglobin.

On reflection:

Q. Considering neuromuscular pathology in the ventilated Critical Care patient, what do you think is the clinician’s responsibility to patients showing evidence of weakness?

A. It is essential to have a strong clinical suspicion for neuromuscular problems, so that ventilatory support can be weaned at a rate appropriate to the patient’s weakness. It is also essential to be aware that neuromuscular pathology may predate ICU admission, but not have been diagnosed. Specific and supportive therapy may be required, depending on the aetiology of the weakness.

The cases presented here further demonstrate that neuromuscular conditions are extremely important in the context of the critically ill patient. They may either cause admission to the ICU or complicate the conditions for which ICU admission was necessary. The clinical examination and investigations required to diagnose these are relatively straightforward. Remember also to consider the importance of communication and the psychological effects of these debilitating conditions on the patient, relatives and staff.