Neurology

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Neurological problems on the ICU

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Intensive care physicians require an increasing input from neurologists, especially with regard to the assessment of hypoxic brain damage and the neurological complications of critical illness, organ failure and sepsis. In contrast, dedicated neurological and neurosurgical intensive care units (ICUs) in neuroscience centres tend to deal with the management of primary diseases of the central and peripheral nervous system which may cause encephalopathy, raised intracranial pressure (ICP), ventilatory, autonomic and bulbar insufficiency or profound neuromuscular weakness.[1–4]

States of impaired consciousness

The assessment of level of consciousness on the ICU may be complex because of the presence of multiple factors relating to the underlying condition and its management. Several different states of impaired consciousness may be recognised (Table 1).

Coma

Coma may be due to many neurological and general medical disorders (Table 2). The clinical assessment of patients with a depressed level of consciousness is summarised in Table 3. Assessment is complicated by the use of sedative and analgesic medication – drugs increasingly used on ICUs and valuable in reducing discomfort, pain, agitation and distress. However, they may have unpredictable effects, particularly after prolonged use in the presence of renal or hepatic failure. Thus, unexplained impairment of consciousness or failure to breathe may be explained by prolonged action of depressant drugs on the central nervous system.[5]

Outcome from coma

Most of the patients who do not die recover from coma within 2–4 weeks; the extent of recovery is highly variable, ranging from vegetative state to full recovery. The prognosis of a patient in coma cannot be assessed with complete accuracy but a number of clinical factors help to guide the observer in predicting the likely outcome (Table 4).

Failure to awaken from a depressed state of consciousness

Following a period of sedation/failure to awaken or persistence of the depressed consciousness state may be due to the underlying neurological insult or an intercurrent event. If prolonged sedation has been excluded, the most common cause is a metabolic encephalopathy, but other factors including hypoxic-ischaemic insults, structural lesions and epilepsy may contribute (Table 5). The diagnosis may be difficult to elicit in an unconscious patient; careful assessment of medication, sepsis, metabolic status and fluid balance is essential.

Metabolic encephalopathy

Central pontine myelinolysis due to rapid changes in plasma sodium and osmolarity is associated with an impaired conscious level, brain stem signs and limb weakness (Fig 1).

Uraemic encephalopathy may occur as a consequence of renal failure, but a

Key Points

- **The assessment of level of consciousness on the ICU may be complex because of the presence of multiple factors relating to the underlying condition and its management**
- **Most patients who do not die recover from coma within 2–4 weeks; the extent of recovery is highly variable, ranging from vegetative state to full recovery**
- **It is not possible to assess the prognosis of a patient in coma with complete accuracy but a number of clinical factors that may be a guide include aetiology, depth and duration of coma, myoclonic status, the computed tomography scan, EEG appearances and the cortical somatosensory evoked potentials**
- **Weakness on the ICU often presents as difficulty in weaning from ventilation, reduced movements in an obtunded patient or generalised or focal weakness in an awake and alert patient**
- **Critical illness polyneuropathy is an acute sensorimotor axonal neuropathy developing in the setting of systemic inflammatory response syndrome and/or multi-organ failure. It is self-limiting, with the overall prognosis influenced by the severity of the underlying condition**

KEY WORDS: coma, critical care, critical illness polyneuropathyn, encephalopathy

similar clinical pattern can also develop following treatment in dialysis dementia and the dialysis disequilibrium syndrome. The clinical features are non-specific, with fatigue, insomnia, pruritis and progressive cognitive impairment, culminating in asterixis, tetany, myoclonus, confusion, seizures, stupor and coma.

Hepatic encephalopathy presents with lethargy and coma, leading to somnolence and disorientation associated with an asterixis and fetor. Features of raised ICP and seizures may occur before the development of deep coma.

Hypoxic–ischaemic encephalopathy

In patients with sustained hypoxic-ischaemic brain injury secondary to cardiac arrest, perioperative hypotension, blood loss, shock or any other acute medical emergency it is important to establish an early prognosis to guide management and, in particular, to determine the appropriate level of support and the possibility of recovery or prolonged survival in a profoundly disabled state. In non-traumatic coma, absent brainstem reflexes and motor responses at 24 hours indicate a poor prognosis. However, the following combination of features has complete specificity for poor outcome in all studies of patients with postanoxic coma:[6]

- absent pupillary light reflexes at day three
- bilateral absence of early cortical somatosensory evoked potentials
- isoelectric or a burst suppression pattern on an EEG within the first week.

Sepsis

The systemic inflammatory response syndrome (SIRS) is a severe systemic response occurring in up to 50% of those in a critical care setting in response to infection or other insults such as burns, trauma or surgery (Table 6). Septic encephalopathy (SE) is the most common form of encephalopathy encountered in intensive care medicine

Table 1. States of impaired consciousness.

Clouding of consciousness	State of reduced wakefulness characterised by impaired attention and memory. Patients may be distractable, hyperexcitable and irritable, with slow thought processes
Acute confusional state	Impairment of consciousness in which stimuli are intermittently misinterpreted. Patients are drowsy, bewildered, disorientated in time, have poor short-term memory and comprehension, possibly difficulty undertaking complex tasks and show day-night reversal
Delirium	Floridly abnormal mental state with disturbed consciousness, disorientation, severe motor restlessness, fear, irritability, consistent misperception of sensory stimuli and visual hallucinations. There may be lucid periods. Patients are often agitated, irritable, suspicious and talkative
Obtundation	Mental blunting with apathy and inactivity. Patients are drowsy, hypersomnolent with reduced alertness and lessened interest in the environment
Stupor	Similar to deep sleep, from which the patient can be aroused only by vigorous and repeated stimuli. Even when aroused, communication is by monosyllabic sounds and simple behaviours. When the stimulus ceases, the stuporous subject lapses back into the unresponsive state
Coma	State of unrousable unresponsiveness in which the subject lies with his or her eyes closed. There is no understandable response to external stimuli or inner need and total absence of awareness of self and environment even when the subject is externally stimulated
Vegetative state	Patients appear to be awake with their eyes open, but show no evidence of awareness of self or environment, are unable to interact with others and have no evidence of purposeful or voluntary behavioural responses to visual, auditory, tactile or noxious stimuli. Sleep-wake cycles are preserved, as are hypothalamic and brainstem autonomic responses. The vegetative state develops after a variable period of coma; it may be partially or totally reversible or may progress to a permanent vegetative state or death

Table 2. Causes of coma.

Without focal or lateralising signs or meningism	Drugs, toxins and poisons Hypoxic-ischaemic encephalopathy Endocrine: diabetes, thyroid, adrenal Metabolic: renal, hepatic, electrolyte, thiamine Systemic infection Seizures
Meningism without focal or literalising signs	Subarachnoid haemorrhage Meningitis Encephalitis
Focal lateralising hemispheric signs (symmetrical or asymmetrical)	Trauma Vascular: infarction, haemorrhage, venous Tumour Infection: abscess Demyelination: multiple sclerosis, acute disseminated encephalomyelitis
Focal brainstem signs	Herniation Trauma Vascular: posterior circulation Tumour Infective: brainstem encephalitis Demyelination

(50–70% of septic patients) and is characterised by slowing, disorientation, delirium, impaired consciousness or coma. There may also be rigidity, tremors and seizures. It is difficult to separate the outcomes attributable to SE and to the precipitating condition and coexisting renal and hepatic impairment. SE is potentially reversible: the aims of management are treatment of the underlying source of sepsis and supportive intensive care.[7,8]

Involuntary movements

Tonic-clonic or other stereotyped movements occur as a manifestation of generalised or focal seizures or epilepsia partialis continuans.

Myoclonic jerking (non-rhythmic jerking movements in single or multiple muscle groups) is seen with anoxic encephalopathy, metabolic coma (eg hepatic encephalopathy) and occasionally following pontine infarction.

Myoclonic seizures typically lack a tonic component. They may be precipitated by touch, tracheal suction or loud hand clapping and can involve facial muscles and other axial structures.

Seizures

Seizures on the ICU are usually focal but may be generalised motor convulsions and, in fact, all seizure types occur[9] (common precipitants are shown in Table 7). It is essential to diagnose the seizure type and ensure early, appropriate treatment and differentiation from metabolic myoclonus and extrapyramidal movement disorders. Non-convulsive status epilepticus is common and a poorly recognised cause of coma.[10]

Table 3. Clinical assessment of patients in coma.

1	Resuscitation and emergency treatment	
2	Medical assessment	
3	Establish level of consciousness	Eye opening Motor response Verbal output
4	Identify brainstem activity Brainstem reflexes	Pupils Eye movements: Spontaneous Oculocephalic Oculovestibular Corneal reflex and facial movements Bulbar: Cough Gag Respiratory pattern
5	Motor function	Involuntary movements Seizures Muscle tone Motor responses Tendon reflexes

Table 4. Outcome from coma.

Aetiology	Coma associated with drug and alcohol ingestion, metabolic disturbance or trauma generally carries a better prognosis for recovery than with ischaemic or structural causes
Depth of coma	Determined by GCS and the presence or absence of reflexes in the cranial nerve territory – a sensitive guide to outcome, with the best outcome associated with patients who maintain normal brainstem reflexes throughout the acute illness or resuscitation
Duration of coma	Only 12% of patients comatose more than 6 hours after cardiac arrest survive with a good outcome or moderate deficits. If there is no eye opening, vocal response or motor function after 6 hours, the patient has a 6% chance of making a moderate or good recovery
Myoclonic status	Occuring within 12 hours of cardiac resuscitation
CT scan	The presence of cerebral oedema, mass effect, temporal lobe infarction or hydrocephalus implies a worse outlook
EEG	Poor outcome implied if iso-electric or shows burst-suppression or 'alpha coma' (8–12 Hz rhythm)
Cortical somatosensory evoked potentials	Absence suggests poor prognosis

CT = computed tomography; GCS = Glasgow coma scale.

Table 5. Causes of failure to awaken on ICU after sedation or anaesthetic.

- Drugs: sedation, analgesia, neuromuscular paralysis
- Hypoxic: ischaemic injury
- Sepsis
- Metabolic encephalopathy: renal, hepatic, electrolyte, endocrine
- Stroke
- Primary CNS inflammation
- Multifactorial (most common)

CNS = central nervous system.

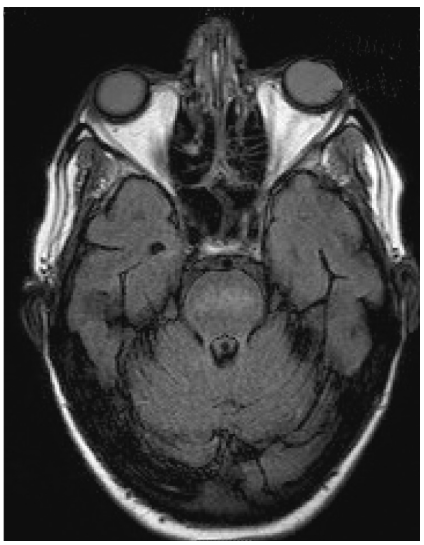

Fig 1. Central pontine myelinolysis showing extensive pontine demyelination (T1-weighted axial magnetic resonance image).

Table 6. Systemic inflammatory response syndrome (SIRS).

SIRS may be suspected in the presence of two or more of the following criteria:	
Temperature	>38°C or <36°C
Heart rate	>90/min
Respiratory rate	>20/min
$PaCO_2$	<32 mmHg
White blood cell count	>12,000 or <4,000 cells/mm^3

Classical ictal signs may be absent and diagnosis depend on the observation of subtle movements of fingers, eyes or lips. The diagnosis should be considered when there is abrupt and unexplained deterioration in conscious level, often following a recognised seizure or an anoxic ischaemic insult with preserved brain stem reflexes. The emergency management of status epilepticus is described in Fig 2.

Myoclonic status usually occurs within 12 hours of cardiac resuscitation and persists for a further 48 hours. These patients are deeply unconscious, with jerking movements involving limbs and face (grimacing and eye opening), typically unresponsive to drug treatment. Myoclonic status is a poor prognostic sign, predicting death or vegetative state in 90% of cases.[11] Some patients who recover from post-anoxic coma may develop late-onset multifocal action and stimulus-sensitive myoclonus which becomes evident as consciousness is regained (Lance-Adams syndrome).[12] This condition responds to treatment with benzodiazepines, piracetam or sodium valproate; it improves with time leaving little or no residual neurological deficit.

Table 7. Causes of partial or generalised status epilepticus.

Acute	Head injury
	CNS infection: encephalitis, meningitis
	Cerebrovascular accident
	Renal failure
	Sepsis syndrome
	Drug toxicity
	Electrolyte imbalance
	Hypoglycaemia
	Hypoxic-ischaemic brain injury
	Pseudo status
Chronic	Pre-existing epilepsy
	Poor anti-epilepsy drug compliance
	Dosage alteration
	Chronic alcoholism/alcohol withdrawal
	Cerebral space-occupying lesion

CNS = central nervous system.

Stroke

Patients may fail to regain full consciousness because they have had a stroke, either at presentation or as a complication of their critical illness or its management. Late clinical deterioration may occur in patients admitted after stroke for several reasons (listed in Table 8).

Weakness and failure to wean from mechanical ventilation

Weakness on the ICU often presents as difficulty in weaning from ventilation, reduced movements in an obtunded patient or generalised or focal weakness in an awake and alert patient (Table 9).[13,14]

Neuropathies

The critical care patient is at risk of developing neuromuscular complications of prolonged ICU care. The most common is critical illness polyneuropathy (CIP) but other causes of neuropathy such as therapeutic agents, nutritional deficiency, acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome (GBS)), acute motor axonal neuropathy and acute intermittent porphyria must be considered (Table 9). GBS may present with multi-organ impairment (eg respiratory failure due to aspiration, or complete heart block) or may develop during the course of a critical illness. The presence of multiple general medical factors and other possible reasons for weakness and failure to wean may lead to failure to recognise the condition.

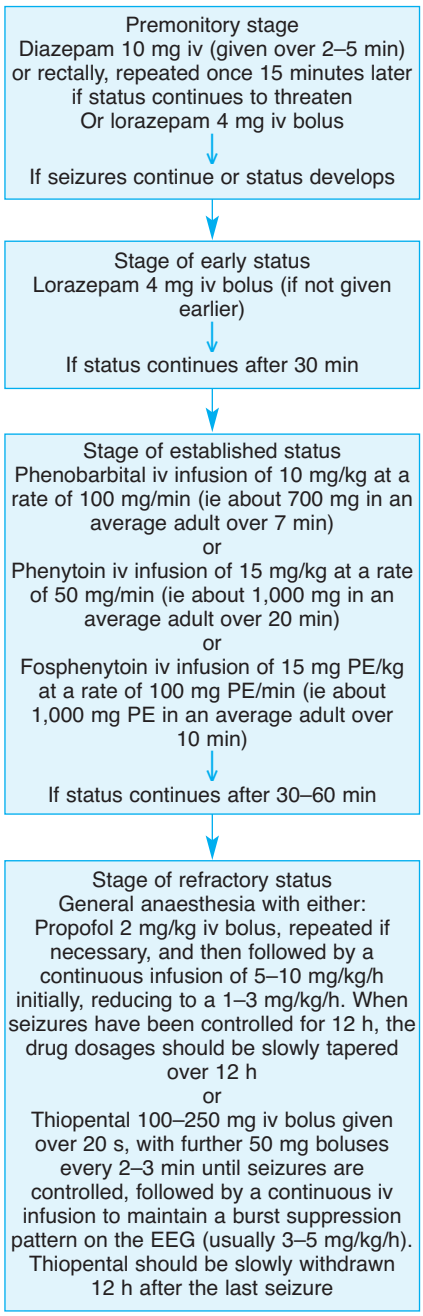

Fig 2. Emergency drug treatment of tonic-clonic status in adults.
iv = intravenous; PE = phenytoin equivalent. Reproduced with kind permission of BMJ Publishing Group Ltd.[9]

Table 8. Causes of late clinical deterioration following stroke.

- Cerebral oedema causing mass effect and shift of the brainstem
- Haemorrhagic conversion of infarction
- Progression of infarction
- Extension of thrombus causing successive occlusion of the perforating arteries
- Emboli arising from the occluded vessel
- Rebleeding into intracerebral haemorrhage
- Intraventricular extension of haemorrhage
- Hydrocephalus due to obstruction of third and fourth ventricles, aqueduct or outflow
- Development of seizures
- Systemic factors:
  - Congestive cardiac failure
  - Pulmonary aspiration, oedema, pulmonary emboli
  - Cardiac arrhythmia
  - Sepsis
  - Complications of a hypercoagulable state

Table 9. Causes of persistent weakness on the ICU: neuromuscular disorders in critical care.

Disorders of the spinal cord	Acute epidural compression due to neoplasm or infection Acute transverse myelitis Cord infarction Other myelopathies (including traumatic) Tetanus
Anterior horn cell	Motor neurone disease Poliomyelitis or post-polio syndromes Rabies
Multiple radiculopathies	Carcinomatous meningitis AIDS polyradiculitis
Acute polyneuropathy	Acute inflammatory demyelinating polyneuropathy Acute motor and sensory axonal neuropathy Critical illness polyneuropathy Other acute polyneuropathies (porphyria, organophosphate poisoning)
Chronic polyneuropathies	Chronic inflammatory demyelinating polyneuropathy Diabetic polyneuropathy
Neuromuscular transmission defect	Myasthenia gravis Lambert-Eaton myasthenic syndrome Neuromuscular blocking agents Other: botulism, toxins, hypermagnesaemia, organophosphate poisoning
Myopathy	Congenital Inflammatory myopathies Myotonic dystrophy Acid maltase deficiency Myopathies associated with neuromuscular blocking agents and steroids (eg AQM) Myopathy and sepsis Cachectic myopathy Others: mitochondrial myopathies, HIV related, sarcoid and hypokalaemic myopathies Rhabdomyolysis Periodic paralysis

AQM = acute quadriplegic myopathy.

Critical illness polyneuropathy

CIP is an acute sensorimotor axonal neuropathy which develops in the setting of SIRS and/or multi-organ failure, particularly in the presence of hyperglycaemia, insulin deficiency and hypoalbuminaemia.[15–18] Up to 70% of patients with sepsis and multi-organ failure develop abnormalities on nerve conduction studies. CIP is characterised by delayed weaning from ventilation, severe flaccid wasting and weakness, and areflexia. Sensory impairment may be seen in patients who are able to cooperate with the examination. However, the signs are variable and difficult to elicit because of sedation or coexistent septic encephalopathy.

CIP is self-limiting but the overall prognosis is influenced by the severity of the underlying condition which accounts for most of the mortality. Recovery may be rapid and complete, but a significant proportion of patients with severe neuropathy requiring axonal regeneration for recovery either do not recover or have a persistent deficit.

Recognition of CIP is important as it may guide ventilatory management and ongoing care. It has been suggested that the condition may be prevented by tight control of glucose levels.[19]

Muscle disease

Muscle disease on the ICU may occur as a consequence of prolonged neuromuscular junction blockade or direct myopathic involvement.[20,21]

Neuromuscular junction blocking agents are increasingly used to facilitate intubation, improve lung compliance, allow more efficient mechanical ventilation and reduce fluctuations in ICP. Non-depolarising neuromuscular blocking agents (eg atracurium, pancuronium, vecuronium) produce longer lasting neuromuscular blockade by reversibly occupying postsynaptic receptors and antagonising acetylcholine.

Prolonged neuromuscular blockade may occur after either short- or long-term blockade with non-depolarising agents

and often occurs if there is coexisting metabolic acidosis, hepatic or renal insufficiency and elevated levels of magnesium. The condition occurs in the context of cumulative doses of neuromuscular junction blocking agents, often given with corticosteroids, aminoglycosides or other anaesthetic agents. Recovery usually occurs within several days of discontinuation of the neuromuscular blocking agent.

Other neuromuscular junction disorders. Previously unrecognised neuromuscular junction disorders can be unmasked by medications commonly used intraoperatively, in the recovery room or ICU. Patients with myasthenia gravis or the Lambert-Eaton myasthenic syndrome have an extremely high sensitivity to subtherapeutic levels of agents such as aminoglycoside antibiotics and certain anti-arrhythmic agents, with minimal effect on neuromuscular transmission in normal persons. Patients may fail to wean from ventilation as a consequence of a number of different forms of myopathic weakness.

Myopathies

Non-necrotic cachectic myopathy is common, manifesting as muscle wasting with associated weakness.

Myopathy with selective loss of thick filaments (myosin) (acute quadriplegic myopathy (AQM))[22–24] is associated with exposure to high doses of glucocorticoids and non-depolarising muscle blocking agents but can also occur following major organ transplantation, particularly liver.[25,26] AQM does not seem to correlate with duration of intensive care. Patients may present as the acute illness resolves when it becomes apparent that they cannot wean from ventilatory support because of a flaccid myopathic quadriparesis. Some patients have only mild weakness, but many are severely affected. Creatine kinase levels are elevated and muscle biopsy confirms some necrosis with loss of thick myosin filament and atrophy.

Acute severe necrotising myopathy may develop after exposure to neuromuscular blocking agents with or without steroid therapy.[27]

Acute steroid myopathy may develop in patients treated with high-dose steroids.

Pyomyositis due to septic micrometastases may result from direct sepsis affecting the muscle.

References

1 Wijdicks EF. *The clinical practice of critical care neurology*. Philadelphia: Lippincott-Raven, 1997.
2 Razvi SS, Bone I. Neurological consultations in the medical intensive care unit. *J Neurol Neurosurg Psychiatry* 2003; 74(Suppl 3):iii16–23.
3 Howard RS, Kullmann DM, Hirsch NP. Admission to neurological intensive care: who, when, and why? Review. *J Neurol Neurosurg Psychiatry* 2003;74(Suppl 3): iii2–9.
4 Howard RS, Radcliffe J, Hirsch NP. General medical care on the neuromedical intensive care unit. Review. *J Neurol Neurosurg Psychiatry* 2003;74(Suppl 3):iii10–15.
5 Jacobi J, Fraser GL, Coursin DB *et al.* Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002;30:119–41.
6 Geocadin RG, Buitrago MM, Torbey MT *et al.* Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. *Neurology* 2006;67:105–8.
7 Evans TW. Haemodynamic and metabolic therapy in critically ill patients. *N Engl J Med* 2001;345:1417–8.
8 Davies NW, Sharief MK, Howard RS. Infection-associated encephalopathies: their investigation, diagnosis and treatment. *J Neurol* 2006;253:833–45.
9 Shorvon S. The management of status epilepticus. *J Neurol Neurosurg Psychiatry* 2001;70(Suppl 2):ii22–7.
10 Towne AR, Waterhouse EJ, Boggs JG *et al.* Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000;54:340–5.
11 Wijdicks EF, Young GB. Myoclonus status in comatose patients after cardiac arrest. *Lancet* 1994;343:1642–3.
12 Morris HR, Howard R, Brown P. Early myoclonic status and outcome after cardiorespiratory arrest. *J Neurol Neurosurg Psychiatry* 1998;64:267–8.
13 Lacomis D, Petrella JT, Giuliani MJ. Causes of neuromuscular weakness in the intensive care unit: a study of ninety-two patients. *Muscle Nerve* 1998;21:610–7.
14 Gorson KC. Approach to neuromuscular disorders in the Intensive Care Unit. *Neurocritical Care* 2005;3:195–212.
15 Hughes RA, Cornblath DR. Guillain-Barré syndrome. Review. *Lancet* 2005;366:1653–66.
16 Hund E. Critical illness polyneuropathy. Review. *Curr Opin Neurol* 2001;14:649–53.
17 Visser LH. Critical illness polyneuropathy and myopathy: clinical features, risk factors and prognosis. *Eur J Neurol* 2006;13: 1203–12.
18 Bolton CF. Neuromuscular manifestations of critical illness. *Muscle Nerve* 2005;32:140–63.
19 Hermans G, Wilmer A, Meersseman W *et al.* Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respirat Crit Care Med* 2007;175:480–9.
20 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 11-1997. A 51-year-old man with chronic obstructive pulmonary disease and generalized muscle weakness. *N Engl J Med* 1997;336:1079–88.
21 Hudson LD, Lee CM. Neuromuscular sequelae of critical illness. *N Engl J Med* 2003;348:745–7.
22 Lacomis D, Giuliani MJ, Van Cott A, Kramer DJ. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. *Ann Neurol* 1996;40: 645–54.
23 Lacomis D, Zochodne D, Bird SJ. Critical illness myopathy. *Muscle Nerve* 2000;23:1785-8.
24 Murray MJ, Brull SJ, Bolton CF. Brief Review: Nondepolarizing neuromuscular blocking drugs and critical illness myopathy. *Can J Anaesth* 2006;53:1148–56.
25 Campellone JV, Lacomis D, Kramer DJ, Van Cott AC, Giuliani MJ. Acute myopathy after liver transplantation. *Neurology* 1998; 50:46–53.
26 Wijdicks EE, Litchy WI, Weisner RH, Krom RA. Neuromuscular complications associated with liver transplantation. *Muscle Nerve* 1996;19:696–700.
27 Zochodne DW, Ramsay DA, Saly V, Shelley S, Moffatt S. Acute necrotizing myopathy of intensive care: electrophysiological studies. *Muscle Nerve* 1994; 17:285–92.