Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis

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Critical illness polyneuropathy (CIP) and myopathy (CIM) are complications of critical illness that present with muscle weakness and failure to wean from the ventilator. In addition to prolonging mechanical ventilation and hospitalisation, CIP and CIM increase hospital mortality in patients who are critically ill and cause chronic disability in survivors of critical illness. Structural changes associated with CIP and CIM include axonal nerve degeneration, muscle myosin loss, and muscle necrosis. Functional changes can cause electrical inexcitability of nerves and muscles with reversible muscle weakness. Microvascular changes and cytopathic hypoxia might disrupt energy supply and use. An acquired sodium channelopathy causing reduced muscle membrane and nerve excitability is a possible unifying mechanism underlying CIP and CIM. The diagnosis of CIP, CIM, or combined CIP and CIM relies on clinical, electrophysiological, and muscle biopsy investigations. Control of hyperglycaemia might reduce the severity of these complications of critical illness, and early rehabilitation in the intensive care unit might improve the functional recovery and independence of patients.

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Introduction

In the early 1980s, when first described, critical illness polyneuropathy (CIP) seemed to be a very rare complication of sepsis and multiorgan failure.[1] However, the past 25 years of research have shown that CIP affects between a third and half of the most severely critically ill patients, and is the most frequent acute polyneuropathy in intensive care units (ICU). CIP presents with limb and respiratory muscle weakness and is strongly associated with failed weaning of patients from the ventilator; despite improvement, patients have varying degrees of disability after discharge from the acute care hospital. The muscles can be primarily involved without the nerves necessarily being affected.[2] Early names for this primary myopathy were acute quadriplegic myopathy, critical care myopathy, acute necrotising myopathy of intensive care, thick filament myopathy, critical illness myopathy, acute corticosteroid myopathy, acute hydrocortisone myopathy, acute myopathy in severe asthma, and acute corticosteroid and pancuronium associated myopathy. Critical illness myopathy (CIM) is now deemed to be the appropriate term.[3–5]

Increasingly, survivors of critical illness are being recognised as a population with profound residual disability.[6] Many survivors of critical illness complain of weakness for months to years after discharge from hospital[7] and have persistent exercise limitations.[8–10] Although the cause might be multifactorial,[5] CIP and CIM have a major role and clinical neurologists should be familiar with the diagnosis of these disorders.

Diagnosis of CIP and CIM is difficult in the ICU, because either the pre-existing disorder or complications arising during the ICU stay can cause muscle weakness. Moreover, the patient's condition might preclude careful clinical examination, and the attention of the physician when the patient is first admitted to intensive care will be directed towards survival, thus delaying diagnosis of CIP and CIM. Electrophysiological investigations of peripheral nerves and muscles can help to achieve diagnosis of CIP and CIM at an early stage and to define prognosis, but they are time consuming and need skilled personnel. Therefore, a guided approach to diagnosis is valuable. Management of CIP and CIM rests on supportive treatment, treatment of ongoing sepsis and multiorgan failure, and control of hyperglycaemia. Recent evidence suggests that early rehabilitation can be safely and effectively implemented in the ICU to maintain patients' physical function, provided that patients are given little or no sedation.

In this Review, we describe the incidence, major risk factors, and the clinical, electrophysiological, and histological features of CIP and CIM. We present a diagnostic flowchart for an ordered approach to clinical and electrophysiological testing. We also discuss the major advances in early rehabilitation and protocols of little or no sedation in the ICU, which effectively improve the functional independence of patients.

Critical illness polyneuropathy

Clinical features

CIP is a distal axonal sensory-motor polyneuropathy affecting limb and respiratory muscles (panel 1).[12] Facial muscles are usually not affected. Limb involvement is

***Panel 1:* Diagnostic criteria for critical illness polyneuropathy**

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. Electrophysiological evidence of axonal motor and sensory polyneuropathy
4. Absence of a decremental response on repetitive nerve stimulation

Definite diagnosis of critical illness polyneuropathy is established if all four criteria are fulfilled. Probable diagnosis of critical illness polyneuropathy is established if criteria 1, 3, and 4 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. Modified from Bolton,[11] by permission of John Wiley & Sons.

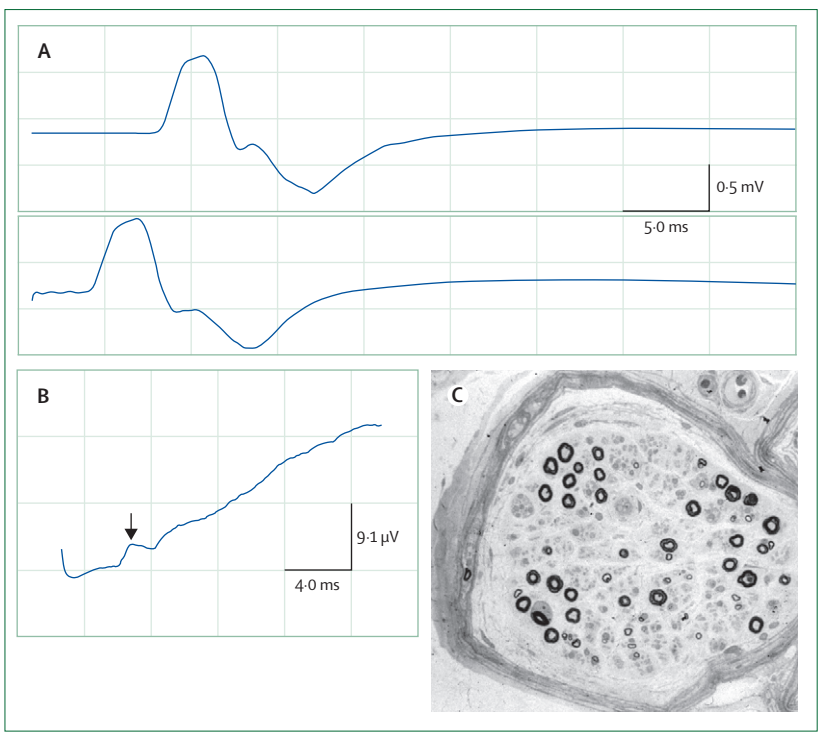

Figure 1: **Critical illness polyneuropathy**
(A) Compound muscle action potential from the thenar muscle on stimulation of the median nerve at the elbow (upper trace) and at the wrist (lower trace). The latencies are normal, but the amplitude is markedly reduced, to 0·7 mV, which is typical of axonal degeneration. The duration of 4·9 ms is in the normal range (3·0–7·8),[21] typical of critical illness polyneuropathy. Image courtesy of Michel Melanson, Queen's University, Kingston, ON, Canada. (B) Sural nerve action potential. This was recorded with a needle inserted near the nerve (owing to tissue oedema, there was no response from surface recordings). The low amplitude, 3·4 μV, and near normal latency, 3·9 ms, is typical of the axonal degeneration of sensory fibres in critical illness polyneuropathy. Adapted from Bolton and colleagues,[12] by permission of BMJ Publishing Group. (C) Light microscopic image, using toluidine blue stain, of sural nerve biopsy showing axonal degeneration with decreased density of myelinated fibres, magnification ×150.

symmetrical; it is most prominent in the lower extremities and can be severe. When less severe, muscle weakness is usually more pronounced distally than proximally.

CIP is often preceded by septic encephalopathy.[13] In this disorder, the level of consciousness deteriorates. Because encephalopathy is not usually structural,[14] recovery can be rapid, and difficulty in weaning from mechanical ventilation or obvious weakness of limb movements will be the first signs to be noted during this period. However, even if the patient is sedated or has septic encephalopathy, CIP might be suspected. When the nail bed is compressed to induce a painful stimulus to gauge the level of consciousness, there will be facial grimacing but reduced or absent movement of limbs. Deep tendon reflexes might be preserved at this stage and sensory testing is unreliable.[11] If the patient is alert, distal loss of detection of pain, temperature, and vibration can be recorded.[11] Failure to wean from the ventilator is common, and can be the prevailing symptom.[15] Indeed, CIP is an independent risk factor for failed weaning from the ventilator and prolonged mechanical ventilation.[16]

In a patient who is alert, muscle strength can be tested in functional limb muscle groups with the Medical Research Council (MRC) scale or handgrip dynamometry.[17] Individual MRC scores can be combined into a sum score, which yields an overall estimation of motor function. A score of less than 48 defines ICU-acquired paresis[18] and is associated with prolongation of mechanical ventilation and length of stay in ICU, increased mortality, and reduced quality of life in survivors of critical illness.[9,10,16–19] Respiratory muscle strength can be tested by measurement of the maximal inspiratory and expiratory pressures and vital capacity. Low scores on these measures are correlated with limb muscle weakness, and are associated with delayed extubation, prolonged ventilation,[19] and unplanned readmission to the ICU.[20]

Electrophysiological and histological features

Nerve conduction studies in patients with CIP show a reduction in amplitude of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) with normal or mildly reduced nerve conduction velocity (panel 1, figure 1). By contrast with CIM, CMAP duration is not prolonged. Varying degrees of fibrillation potentials and positive sharp waves will be recorded in both CIP and CIM. Motor unit potentials might not be recordable because they cannot be activated if consciousness is depressed; however, if present, they can be normal or mildly myopathic, hence the distinction between CIM and CIP is not clear. As recovery occurs in CIP, fibrillation potentials and positive sharp waves tend to be lost and motor unit potentials become polyphasic as a sign of reinnervation of muscle. In time they increase in amplitude.[11]

Comprehensive autopsy studies of the CNS and peripheral nervous system, particularly of many samples of peripheral nerve and muscle, have confirmed electrophysiological findings of a primary distal axonal degeneration of motor and sensory fibres (figure 1).[2,15] Denervation atrophy of muscle results. The only pronounced CNS abnormality is chromatolysis of anterior horn cells, indicating damage to the axon of the cell body.[15]

Muscle biopsy in CIP will show evidence of acute denervation of muscle with atrophy of both type 1 and type 2 fibres. Later in the course of CIP, while recovery is ongoing, muscle biopsy will show grouped atrophy of the muscle fibres.[2,15] Nerve biopsy might show signs of axonal neuropathy if done later in the course of critical illness (figure 1),[2] but is rarely indicated in these patients.

Critical illness myopathy

Clinical features

CIM is a primary myopathy that is not secondary to muscle denervation, with distinctive electrophysiological and morphological findings (panel 2, figure 2).[3,4] The clinical features are often much the same as for CIP, with difficulty in weaning from the ventilator, flaccid limbs, and possible reduction in deep tendon reflexes but, if testable, normal sensation.

Electrophysiological and histological features

Major features are abnormal reduction in the amplitude of CMAPs and an increase in their duration, normal SNAPs, reduced muscle excitability on direct stimulation, and myopathic motor unit potentials on needle electromyography (panel 2, figure 2). Reduced muscle membrane excitability is established if the ratio of the CMAP amplitude after nerve stimulation versus that obtained after direct muscle stimulation is less than 0·5, and if the amplitude of CMAP after direct muscle stimulation is less than 3 mV.[22–24]

The duration of the CMAP is an important sign of CIM,[21,25,26] and it accompanies the fall in amplitude. However, the shape of the CMAP is the same for both proximal and distal stimulation of the nerve supplying the muscle (figure 2).[13,25] CMAP duration can be two to three times longer than in healthy controls, and is most pronounced in lower limb nerves.[21,26] Such a change cannot be explained by a neuropathy because, although demyelinating neuropathies can increase duration, this increase is greater with proximal than distal stimulation, and in axonal neuropathies, as in CIP, the duration is not increased. As in CIP, studies of phrenic nerve conduction show reduced amplitude, no change in latency, and presence of fibrillation potentials and positive sharp waves on needle electromyography of the diaphragm.[12] However, motor unit potentials occurring during attempted inspiration normally have a myopathic appearance, so this observation might be unhelpful to distinguish neuropathy from myopathy.[12]

On muscle biopsy, selective loss of thick filaments (myosin) and varying degrees of necrosis are the most common findings (figure 2, table).[2,28] During recovery in CIM, electrophysiological studies will show a rise in the CMAP amplitude and a return to normal duration, loss of fibrillation potentials and positive sharp waves from muscle, and more normal appearing motor unit potentials. On muscle biopsy, there will be gradual loss of necrosis and return of thick myosin filaments.

Combined CIP and CIM

Combined CIP and CIM, which is usually mild but occasionally severe, could be the most common manifestation of neuromuscular weakness in the ICU.[2,23,24,29] In mild forms, electrophysiologically, CMAPs can be reduced, with possibly only borderline abnormalities in the duration of the CMAP and in recording of SNAPs. Needle electromyography studies of muscle might show only a few fibrillation potentials[30] and positive sharp waves, and normal or mildly myopathic motor unit potentials. Muscle biopsy is usually normal. The outlook for recovery in these patients is usually good. In severe forms, electrophysiological studies show great reductions in CMAP amplitudes. SNAPs are usually unrecordable. If still recordable, latencies are minimally affected, suggesting axonal degeneration of sensory nerve fibres.

***Panel 2:* Diagnostic criteria for critical illness myopathy**

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. CMAP amplitudes less than 80% of the lower limit of normal in two or more nerves without conduction block
4. Sensory nerve action potential amplitudes more than 80% of the lower limit of normal
5. Needle electromyography with short duration, low-amplitude motor unit potentials with early or normal full recruitment, with or without fibrillation potentials in conscious and collaborative patients; or increased CMAP duration or reduced muscle membrane excitability on direct muscle stimulation in non-collaborative patients
6. Absence of a decremental response on repetitive nerve stimulation
7. Muscle histopathological findings of primary myopathy (eg, myosin loss or muscle necrosis)

Definite diagnosis of critical illness myopathy is established if all seven criteria are fulfilled. Probable diagnosis of critical illness myopathy is established if criteria 1 and 3–6 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. CMAP=compound muscle action potential. Modified from Lacomis and colleagues,[4] by permission of John Wiley & Sons.

Muscle biopsy shows substantial, generalised necrosis. In the severe form, recovery might not happen or might require prolonged rehabilitation.[4,28]

Effect on outcome

CIP and CIM can cause prolonged severe disability after critical illness. There is substantial evidence that CIP and CIM cause limb and diaphragm weakness that persist for months or years after resolution of critical illness.[8,31–34] As a result, nearly a third of patients with CIP, CIM, or both do not recover independent walking or spontaneous ventilation.[35] Muscle weakness is only one of several contributors to disability after critical illness, but it is by no means the least important. The effect of critical illness and ICU stay can be seriously debilitating.[7] CIP is the main contributor to persistent disability, whereas CIM can be associated with complete recovery. Findings from the 1-year follow-up in the CRIMYNE study showed that severity of muscle weakness was not correlated with clinical and electrophysiological diagnosis, but rapidity and completeness of recovery were. Patients with CIM recovered within 6 months, whereas those with CIP had a slower recovery, or did not recover.[33] Mortality might be increased in patients with CIP.[8,36]

Incidence and risk factors

Exact incidence of CIP and CIM is unknown because of wide variation in the patient population, risk factors, and the diagnostic criteria used, and in the timing of assessment.[37] In patients with mechanical ventilation of

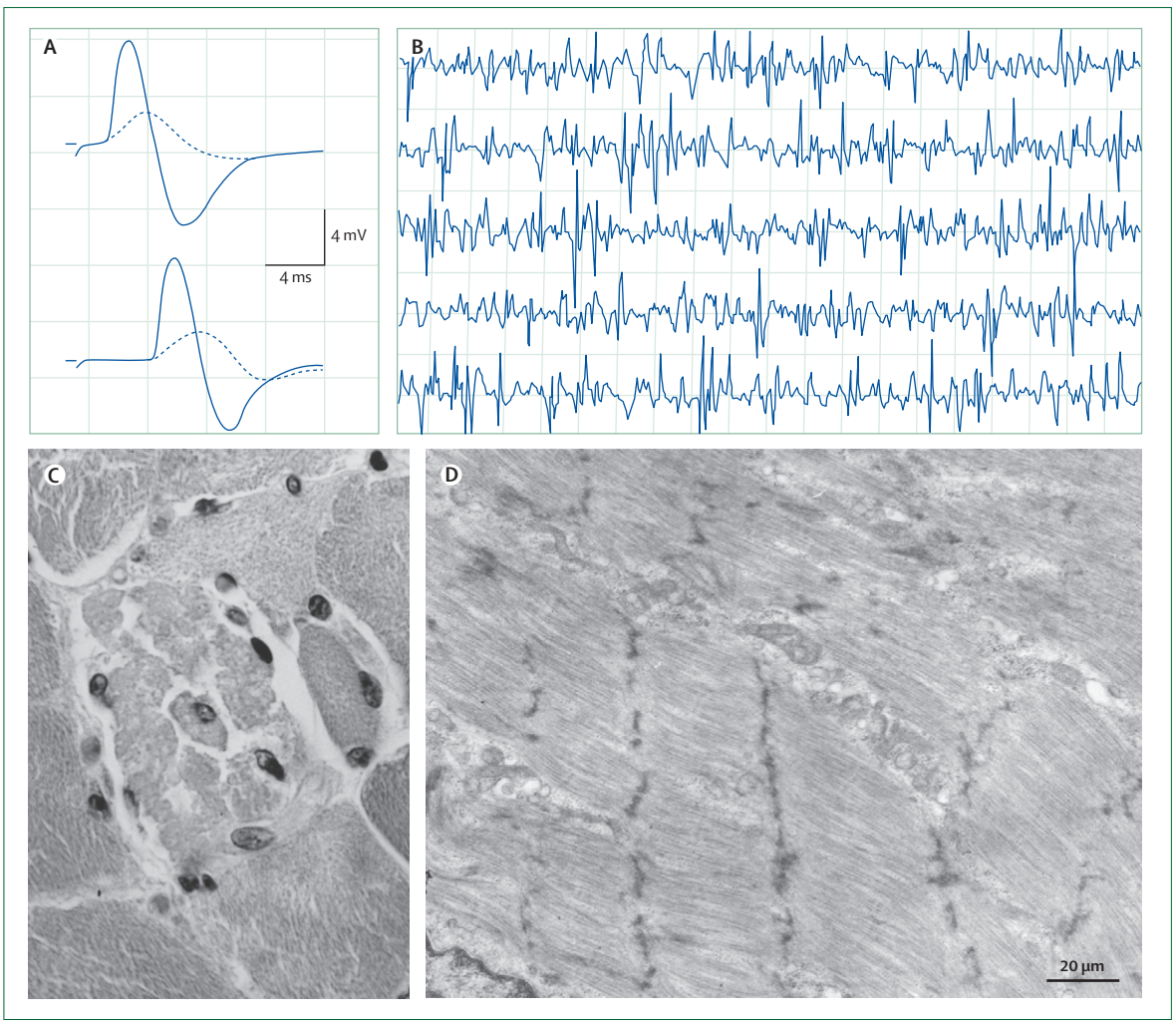

Figure 2: **Critical illness myopathy**
Compound muscle action potential recording from the thenar muscle on stimulation of the median nerve at the wrist and elbow, at the onset of sepsis (A, solid line) and 3 weeks later (B, dotted line). Note the marked drop in amplitude and mild but definite increase in duration without a change in latency. Modified from Bolton,[14] by permission of Elsevier. (B) Needle electromyography of the tibialis anterior muscle. Motor unit potentials have quite low amplitude and short duration, and are highly polyphasic, typical of a myopathy (calibration, 0·1 mV, 10 ms/div). (C) Light microscopic image, using haematoxylin and eosin stain, of open biopsy of the tibialis anterior muscle showing necrotic muscle fibres, magnifcation x300. Image courtesy of David Ramsay, University of Western Ontario, ON, Canada. (D) Electron microscopic image showing needle biopsy of the quadriceps muscle. Thick filaments (myosin) are deficient in all sarcomeres, typical of a myosin deficient myopathy. Image courtesy of Robert Hammond, University of Western Ontario, ON, Canada.

4–7 days' duration[18,38] or with increased risk of developing multiorgan failure, the incidence was 25–33% on clinical assessment[16,18,38] and 30–58% with electrophysiological assessment.[8,39,40] Incidence was 34–60% in patients with acute respiratory distress syndrome,[41,42] 24–77% in those with a lengthy (>1 week) ICU stay,[43–46] 56–80% in those with multiorgan failure with or without sepsis or systemic inflammatory response syndrome (SIRS),[29,36,47,48] and 100% in those with septic shock[49] or severe sepsis and coma.[2]

Sepsis, SIRS, and multiorgan failure are risk factors for CIP and CIM. A systematic review of published work showed evidence of CIP and CIM in 46% (95% CI 43–49) of adult ICU patients who had lengthy mechanical ventilation, sepsis, or multiorgan failure.[50] Factors that have been identified as independent risk factors in prospective studies are: severity of illness;[38,44] duration of multiple (≥two) organ dysfunction with or without SIRS;[18,48] duration of vasopressor and catecholamine support;[46] duration of ICU stay;[46,47] hyperglycaemia;[44–46] female sex;[18] renal failure and renal replacement therapy;[36] hyperosmolality;[36] parenteral nutrition;[36] low serum albumin;[47] and neurological failure.[37] Aminoglycoside antibiotics have been identified as risk factors in some studies[8,44] but not in others.[18,36,41,45–47,51] Similar conclusions can be drawn in the case of neuromuscular blocking agents and steroids.[52] The neuromuscular blocking agent cisatracurium besylate improves survival and increases the time without ventilation in patients with acute

	Incidence	Clinical features	Electrophysiological findings	Serum creatine kinase	Muscle biopsy	Prognosis
Polyneuropathy						
Critical illness polyneuropathy	Common	Flaccid limbs, respiratory weakness	Axonal degeneration of motor and sensory fibres	Nearly normal	Denervation atrophy	Variable
Neuromuscular transmission defect						
Transient neuromuscular blockade	Common with neuromuscular blocking agents	Flaccid limbs, respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	Good
Critical illness myopathy						
Thick-filament myopathy	Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs, respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Acute myopathy with scattered necrosis	Common	Flaccid limbs, respiratory weakness	Myopathy	Mildly or moderately raised	Scattered necrosis	Variable
Acute myopathy with diffuse necrosis (necrotising myopathy of intensive care)	Rare	Flaccid weakness, myoglobinuria	Severe myopathy	Greatly raised, myoglobinuria	Marked necrosis	Poor
Disuse (cachectic) myopathy	Common	Muscle wasting	Normal	Normal	Normal or type II fibre atrophy	Variable
Rhabdomyolysis	Rare	Flaccid limbs	Near normal	Markedly elevated (myoglobinuria)	Normal or mild necrosis	Good
Combined polyneuropathy and myopathy	Common	Flaccid limbs, respiratory weakness	Indicative of combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

Modified from Bolton,[27] by permission of Springer.

Table: **Generalised neuromuscular disorders associated with critical illness**

respiratory distress syndrome with apparently no effect on muscle weakness and paralysis.[53] In longitudinal studies in patients with this disorder,[9,10] steroids were the main determinant of impaired ability to exercise at 3 months. At 6 months, their effect was lost and the burden of illness acquired during the ICU stay and rate of resolution of illness became the important determinants of exercise capacity.[9]

Immobility has profound effects on skeletal muscle, and is a risk factor for muscle weakness during critical illness. This immobility, despite profound muscle weakness and wasting, is characterised by normal motor and sensory nerve conduction studies and needle electromyography of muscle (table). Duration of mechanical ventilation as a proxy of immobility is independently associated with severe limb weakness[18] or electrophysiological evidence of CIP.[46,47] Diaphragmatic weakness, injury, and atrophy develop rapidly during mechanical ventilation, and are significantly correlated with the duration of this treatment.[54]

Pathophysiological mechanisms

One unexplained aspect of electrophysiological changes of peripheral nerves and muscles during critical illness is their rapid onset within hours of normal action potential generation[39] and their reversibility.[55] Onset of clinical signs can also be rapid and reversible.[56] The histological appearance of failing nerves and muscles can be normal or provide evidence of minimal muscle necrosis.[2,28] These findings suggest that the defect is mainly functional,[2] as it is for other failing organs.[57] CIP and CIM are not isolated events, but rather are an integral part of the process leading to multiorgan dysfunction and failure. Therefore, shared microcirculatory, cellular, and metabolic pathophysiological mechanisms are likely. During critical illness, microcirculation is impaired throughout the body (ischaemic hypoxia).

Mitochondrial function is impaired with reduced ATP biosynthesis, energy generation, and use (cytopathic hypoxia), which is thought to be a cause of cellular and organ dysfunction in critical illness.[58,59] Metabolic changes include increased secretion of stress hormones, cytokines, and nitric oxide, causing insulin resistance with hyperglycaemia.[57] At a later stage, direct mitochondrial inhibition by nitrogen and oxygen reactive species, and reduced hormonal stimulation and decreased positive feedback from decreased metabolic demands, all combine to reduce energy production.[57] Excitable tissues, such as peripheral nerves and muscle, that spend much of their energy on maintaining function are key targets, and are probably damaged by a combination of ischaemic and cytopathic hypoxia.

There is no direct evidence that microcirculation is impaired in peripheral nerves of patients with CIP. However, Bolton[11] proposed that microcirculatory changes would have a key role in causing distal axonopathy. Expression of E-selectin, a marker of endothelial cell activation, is increased in the vascular endothelium of epineurial and endoneurial vessels of patients with CIP.[60] This increased expression could activate leucocytes within the endoneurial space, with local cytokine production, increased microvascular permeability, and formation of endoneurial oedema. Hyperglycaemia and hypoalbuminaemia[47] can further enhance endoneurial

oedema.[37] Hyperglycaemia can impair the microcirculation to peripheral nerves, which might explain the improvement in CIP that occurs with intensive insulin therapy.[11,46] This combination of events could explain a condition of bioenergetic failure with consequent axonal degeneration.[11,39,47]

In a rat model, an acquired channelopathy with sodium channel inactivation was a relevant mechanism in the pathogenesis of CIP, resulting in rapid and reversible hypoexcitability or inexcitability of nerves.[55] Thus, in some patients CIP might be due to abnormality in nerve excitability in advance of, or possibly without, axonal nerve degeneration. These patients are predicted to have a good outlook, compared with those developing true axonal degeneration.[55] A shift in the voltage dependence of sodium channel fast inactivation towards more negative potentials seems to be the dominant factor, although a reduced density of functional sodium channels cannot be ruled out.[55] Correlation with results of studies in humans remains to be elucidated. Z'Graggen and colleagues[61] have shown that the peripheral nerves of critically ill patients with CIP are depolarised and that this membrane depolarisation is related to endoneurial hyperkalaemia or hypoxia, or both. Whether these cellular events are secondary to microcirculatory events or an inability of the cell to use energy is unknown. Furthermore, whether axonal inexcitability and degeneration are different disorders or merely two processes in the same disorder, with inexcitability being a reversible event preceding axonal degeneration in the case of persisting hypoxia, is unclear.[55,62]

Muscle microcirculatory changes during critical illness are well documented. Density of perfused capillaries of striated muscles is heterogeneously reduced and the number of non-perfused capillaries is increased in animals and people with severe sepsis.[63,64] These microcirculatory changes resolve rapidly in response to therapy in survivors, but persist in patients dying during acute circulatory failure or later from multiorgan failure.[65]

Muscle wasting is a prominent feature of sepsis, and is thought to result from increased muscle protein breakdown.[66] Degraded proteins are transported to the liver, where they have essential roles, such as providing energy, and synthesising glutathione and acute phase proteins.[3] Degraded muscle proteins come mainly from myofibrillar proteins (actin, myosin), which represent 60–70% of muscle proteins, and result in loss of myosin filaments, disorganisation of sarcomeres, and muscle atrophy.[66] Proteases such as calpain and the ubiquitin–proteasome complex have a key role in muscle protein breakdown, although their sequential activation is not well clarified. Myofibrillar proteins are thought to be degraded by a two-step process. Initially, calpains and caspases cleave a small number of key contractile proteins, followed by activation of the ubiquitin–proteasomal degradation pathway and degradation of myofibrillar proteins. Evidence of increased calcium release from the sarcoplasmic reticulum associated with increased calpain activity lends support to the theory of a key role of calcium-dependent proteins in initiating muscle protein breakdown and triggering muscle pathological changes in CIM.[67] However, in a rat ICU model of prolonged mechanical ventilation and pharmacological paralysis, early activation of the ubiquitin–proteasome pathway led to partial or complete loss of muscle myosin, whereas calpain activation was recorded after only 9–14 days of exposure to the ICU condition.[68] Mechanisms of muscle fibre necrosis are unknown, but upregulation of calcium handling proteins might be crucial.[67]

Skeletal muscle immobility can contribute substantially to muscle wasting even in the absence of systemic inflammatory changes.[69] Muscle atrophy begins within hours of bed rest or deep sedation, and even healthy people can have large loss of muscle mass and strength within 10 days of bed rest, particularly from the lower limbs.[70] Mechanical ventilation as a proxy of diaphragmatic immobility is a key trigger leading to diaphragm weakness, especially if combined with sedation.[71]

In patients with septic shock, severity of shock is associated with muscle mitochondrial dysfunction, ATP depletion, intracellular antioxidant depletion, and nitric oxide production.[72] Muscle ATP concentration was significantly lower in septic non-survivors than in either septic survivors or controls, suggesting bioenergetic failure as an important common pathophysiological mechanism for muscle and multiorgan dysfunction.[72] Furthermore, restoration of mitochondrial biogenesis, which maintains normal mitochondrial number, structure, and function and is reduced in bacterial sepsis, is an important factor favouring survival.[73]

Electrical inexcitability of muscle has been shown in models of rat denervation and steroid administration.[74] A change in NaV1·4 sodium channels, with a shift in the voltage dependence of sodium channel fast inactivation towards more negative potentials and depolarisation of resting membrane potential, are the major causal mechanisms.[75,76] Resting membrane depolarisation is ascribed to muscle inactivity, and could be an important mechanism to explain the profound muscle strength reduction during immobility.[77] Upregulation of NaV1·5 sodium channels has been shown in rat muscle with chronic sepsis, suggesting that several risk factors concur in causing electrical muscle inexcitability.[78] A negative shift in sodium channel gating in peripheral nerves, as in muscles supports a unifying hypothesis of CIP and CIM as different manifestations of one disorder.[77]

Diagnosis

ICU staff will have difficulty in weaning some patients who are critically ill from mechanical ventilation (panel 1 and panel 2), which cannot be explained by increased respiratory or cardiac load, metabolic disturbances,

nutritional disorders, profound anaemia, or delirium.[79] When sedation is withdrawn in patients with CIP or CIM, staff might note that limbs have become weak and flaccid. In patients who are comatose, a painful stimulus will induce facial grimacing, but little limb movement. Tendon reflexes might be preserved, and sensory testing is unreliable. Nevertheless, CIP or CIM should be suspected, and if weakness fails to improve, electrophysiological studies and muscle biopsy (either open or needle) usually indicate CIP, CIM, or other neuromuscular complications (table, figure 2). Follow-up studies are often helpful to document improvement or deterioration. Thus, in the early stages features might suggest CIM, but later studies more often indicate CIP. Diagnosis of CIP, CIM, or combined CIP and CIM therefore relies on clinical, electrophysiological, and muscle biopsy investigations.[2,5,11,15,35]

Differential diagnosis

CIP and CIM are complications arising after the onset of critical illness, usually after admission to the ICU. Several disease processes involving the brain, spinal cord, peripheral nerves, neuromuscular transmission, or muscles can cause muscle weakness or paralysis in a patient who is critically ill.[80] Ionic abnormalities such as hypokalaemia and hypophosphataemia can cause acute myopathic processes; hypermagnesaemia can impair neuromuscular transmission. Sepsis by itself does not cause a defect in neuromuscular transmission; however, several drugs can affect neuromuscular transmission, including neuromuscular blocking agents, cancer chemotherapy, statins, and antiretrovirals,[52,56] and this defect can be detected by electrophysiological neuromuscular transmission studies. Chronic use of other drugs is probably important, and should be assessed on an individual basis.

Propofol infusion syndrome is a syndrome of severe metabolic acidosis, cardiac failure, rhabdomyolysis, renal failure, and hypertriglyceridaemia, which is described in both children and adults after high-dose propofol (5 mg/kg/h) is administered for long periods (>48 h).[81] It occurs in 1·1% of critically ill patients receiving propofol, but individual components of the syndrome are frequently recorded.[82] Incidence of propofol infusion syndrome is high in patients with severe head trauma[83] or acute inflammatory syndromes.[81] In rhabdomyolysis, electrophysiological and muscle biopsy findings are normal or near normal, consistent with rapid and complete recovery.[14] Rhabdomyolysis can extend into acute necrotising myopathy;[14] interruption of propofol infusion at an early stage of the syndrome is important to achieve complete recovery.

Patient history is the most important differential criterion between CIP and Guillain-Barré syndrome, which is an autoimmune polyneuropathy amenable to specific treatment with immunoglobulins or plasmapheresis. In Guillain-Barré syndrome, an infection, most frequently a *Campylobacter jejuni* infection with diarrhoea, often precedes the onset of progressive weakness and sensory disturbances by 2–4 weeks. Inflammatory signs have subsided by the time that neurological signs such as pain, paraesthesias, numbness, and weakness in the limbs become evident. Facial muscles, which are unaffected in CIP, are frequently involved. Differential diagnosis with CIP can be difficult if progression of respiratory failure is rapid.[84] No one clinical or electrophysiological sign reliably differentiates Guillain-Barré syndrome from CIP, particularly in cases of acute motor and sensory-motor axonal variants of Guillain-Barré syndrome. In most cases, the concentration of CSF proteins is much higher in patients with Guillain-Barré syndrome than in those with CIP.[19] Serial electrophysiological investigations are essential to achieve an accurate diagnosis.[85–88]

Patients undergoing surgical interventions can develop axonal neuropathies in the absence of nerve compression, contusion, stretching, or transection.[89] Onset time is within 1 month of surgery. Focal, multifocal, or diffuse patterns are described, with pain and weakness as prominent signs. Inflammatory nerve infiltration, ischaemic nerve injury, and active axonal degeneration are constitutive histopathological features. Critically ill patients might need surgery because of their admitting diagnoses or complications arising during ICU stay. A polyneuropathy arising after a delay or in an area away from the surgical site should suggest postsurgical inflammatory neuropathy, which is amenable to immunomodulatory treatment.

Diagnostic algorithm

Alert, collaborative patients with muscle weakness arising as a complication of critical illness should be assessed clinically with the MRC scale (figure 3). In non-collaborative patients, diagnosis is usually deferred. To decide, clinicians should assess whether diagnosis will affect management or provide useful prognostic information. For example, in comatose patients with primary neurological diseases, such as head trauma or subarachnoid haemorrhage, who develop severe muscle weakness or paralysis after ICU admission, electrophysiological investigations can be done to avoid an unreasonably pessimistic prognosis by identification of CIP or CIM as the cause.[2]

Differential diagnosis between CIP and CIM can be important to gain prognostic information about long-term disability. If differentiation is not possible, a generic diagnosis of critical illness neuromyopathy can be acceptable.[90] In addition to electrophysiological study, muscle biopsy can be valuable to distinguish CIP from CIM,[2,29,91] and for determining prognosis. Needle biopsy of muscle can be readily done under local anaesthaesia in the ICU, and the results can be equally as informative as those from an open biopsy. Thus, severe CIP and necrotising CIM can have a poor prognosis, whereas

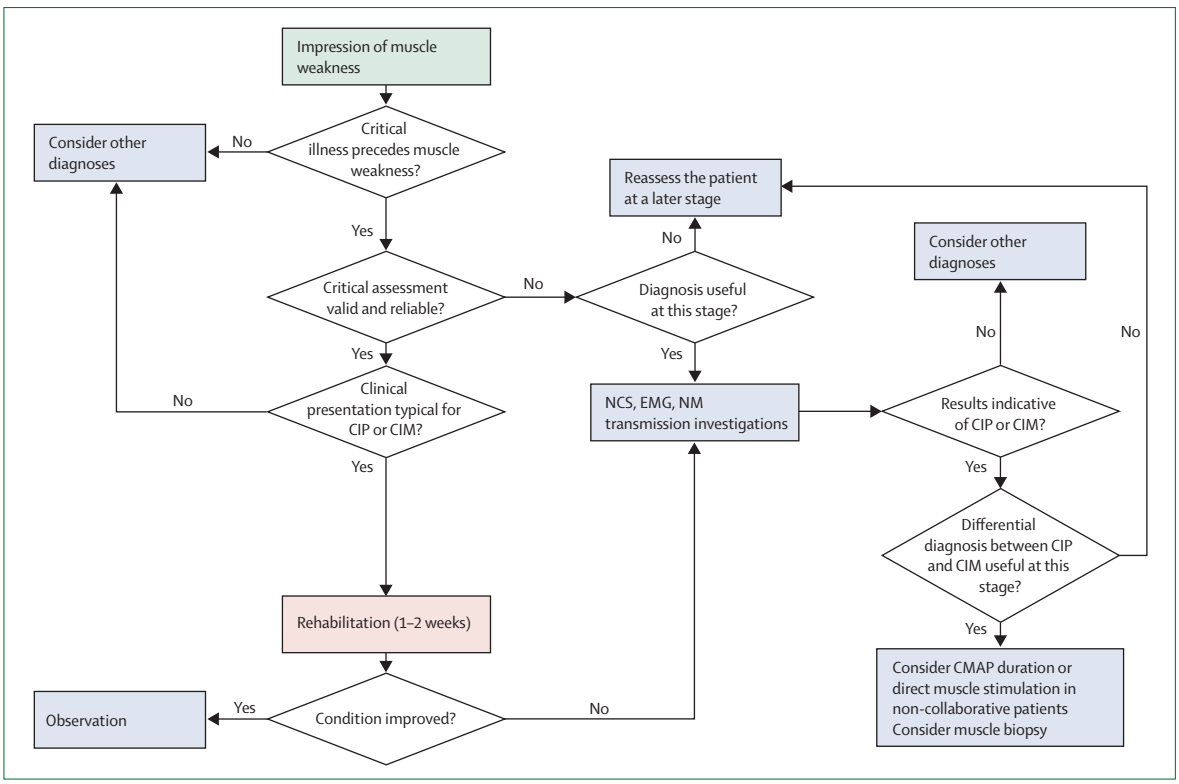

Figure 3: **Diagnostic algorithm**
Typical clinical presentation for CIP and CIM includes symmetrical limb weakness and facial sparing. Modified from Stevens and colleagues,[5] by permission of Wolters Kluwer Health. NCS=nerve conduction study. EMG=electromyography. NM=neuromuscular. CIP=critical illness polyneuropathy. CIM=critical illness myopathy. CMAP=compound muscle action potential.

rhabdomyolysis, disuse myopathy, and thick filament myopathy usually have a much better prognosis (table).

Management

No specific treatment—including nutritional, antioxidant, hormonal therapy, and immunoglobulins—has been shown to reduce the incidence and severity of CIP and CIM.[52] Intensive insulin therapy to maintain normal blood glucose concentrations (4·4 to 6·1 mmol/L) reduces the incidence of electrophysiologically diagnosed CIP and the need for lengthy mechanical ventilation in both surgical and medical patients in the ICU.[45,46] However, the optimum blood glucose target is undetermined,[92] because intensive insulin therapy that is used to promote normoglycaemia increases mortality in adult ICU patients.[93]

Major advances have been made in supportive treatment. Substantial change is in progress in the ICU; a new framework of early rehabilitation has replaced the old view that described rehabilitation as the third phase of medicine and implied that rehabilitation should wait until the patient is clinically stable.[94] Repeated daily passive mobilisation prevents muscle atrophy, as shown by serial muscle biopsies.[95,96] Early physical and occupational therapy in the ICU improves functional independence of patients, although muscle strength is not greatly improved. Additionally, the duration of delirium is shortened, and the number of ventilator-free days is increased compared with standard care.[96] A daily cycle session with a bedside ergometer established early during ICU stay improves functional exercise capacity, quadriceps muscle force, and perceived functional status in patients who survive after care in the ICU.[97] Early rehabilitation should be associated with a policy of reduced or no sedation of critically ill patients—a strategy that has been shown to be effective in randomised controntrolled trials.[98,99] A protocol of coordinated daily interruption of sedatives with spontaneous awakening and interruption of mechanical ventilation with spontaneous breathing trials reduces the duration of mechanical ventilation, coma, and of ICU and hospital stay.[100] 1-year survival is improved; for every seven patients treated with this intervention, one life can be saved.[100] A bundle of ICU measures called ABCDE—Awakening, Breathing, Coordination of awakening and breathing, Delirium assessment and Early exercise—has been proposed for wide application to reduce the burden of both delirium and muscle weakness.[101]

The efficacy of electrical muscle stimulation to improve muscle size and strength has not yet been convincingly shown.[102] Finally, intensive neurorehabilitation after ICU discharge could improve functional recovery and

Search strategy and selection criteria

References for this Review were identified through searches of PubMed from 1982 to July 2011 with the terms: "critical illness myopathy" OR "critical illness polyneuropathy" OR "critical illness polyneuromyopathy" OR ("neuromuscular diseases" [MeSH Terms] AND "intensive care unit"). We supplemented the search with a continuous review of publications in intensive care, neurological, and general medical journals about critical illness myopathy and neuropathy.

independence.[34] However, evidence is from a single-centre uncontrolled series, and needs to be replicated in larger studies with a comparison group.

Conclusions and future directions

CIP and CIM alone or in combination are common complications causing weakness of respiratory and limb muscles in patients who are critically ill. Substantial progress has been made in understanding their pathophysiology. Diagnosis can be achieved at an early stage, prompting control of hyperglycaemia and rehabilitation. Specific diagnosis based on electrophysiological and muscle biopsy investigations can help to establish the prognosis of chronic disability in survivors of critical illness. However, improved animal models of prolonged critical illness, mechanical ventilation, and immobility are needed to improve our understanding of the complex interplay between concurrent pathogentic mechanisms acting at different systemic, tissue, and cellular levels in excitable tissues such as peripheral nerves, muscles, brain, and heart. Prospective cohort studies of representative populations of patients who are critically ill, with accurate diagnosis during the acute stage and comprehensive assessment during long-term follow-up, are needed to clarify prognosis and to validate early electrophysiological changes as an intermediate outcome measure. Improved epidemiological studies of incidence and risk factors would be of great value to define patients who would most benefit from treatments. Lastly, randomised controlled trials of adequate power to detect clinically significant differences in incidence of CIP and CIM and measures of functional independence should be encouraged.

Contributors

Both authors were responsible for the concept of the Review. NL selected the articles to be included and prepared the first draft. Both authors were involved in the writing and editing of the final version of the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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