A syndrome emerged from the description of 5 patients encountered in a 4-year period, who within a month following admission to a critical care unit developed a severe polyneuropathy that included difficulty in weaning from a ventilator and subsequent development of flaccid weakness with areflexia. Although the clinical signs and circumstances were similar to Guillain-Barré syndrome, the cerebrospinal fluid (CSF) examination, electrophysiologic features, and necropsy findings in 3 patients were not. The possibility of either a nutritional deficiency or toxin as the cause was suggested, and as additional cases were identified, this syndrome, polyneuropathy in the critically ill, was soon recognized as being more common than suspected.1–3 Although weakness in the setting of acute illness, particularly sepsis, coma, or burns was described earlier, this report and those that followed were critical in defining a clinical disorder with associated electrophysiologic and pathologic...
features that is now called critical illness neuropathy (CIN). As medical and surgical improvements have led to improved survival of patients who have critical illness, this distinct neuromuscular syndrome is more frequently recognized and reported.

CIN and critical illness myopathy (CIM) are now the most common acquired neuromuscular condition in the intensive care unit (ICU) setting with a risk of development that may reach 50% in patients with sepsis, multiorgan dysfunction syndrome (MODS), or protracted mechanical ventilation, and signs can be seen early. Yet as a syndrome it came somewhat as a surprise that a similar presentation could be caused by muscle dysfunction (CIM) or occurs concurrently with CIN. It has now become clear that there is a spectrum of neuromuscular disorders encountered in the ICU and limited involvement is less common.

Involvement of muscle is defined by clinical and pathologic manifestations as acute quadriplegic myopathy, acute necrotizing myopathy of intensive care or thick filament myopathy, but all those manifestations can be clustered within the term CIM. The recognition of the similarity of clinical syndromes, spectrum, overlapping sites of neuromuscular involvement, and commonality of risk factors or predisposing medical conditions suggests that the proposed term(s) critical illness neuromyopathy (CINM) or critical illness neuromuscular abnormalities (CINMA) as the most encompassing, but eponyms abound and no standardization of nomenclature has yet emerged.

CIN has since been conceptualized as another example of organ system failure attributable to the systemic inflammatory response syndrome (SIRS) that occurs in more than half the patients who have been on mechanical ventilation for more than 1 week and sepsis lasting longer than 2 weeks. SIRS is defined as an inflammatory response to a variety of clinical insults, but manifested by 2 or more of the following conditions: temperature less than 36°C or more than 38°C, heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min or \( P_{aCO_2} \) less than 32 mm Hg and a white blood cell count less than 4000 cells/\( \mu \)L, greater than 12,000 cells/\( \mu \)L, or greater than 10% immature or band forms. Onset of CIN may occur as early as 3 days following onset of sepsis or SIRS; CIN and CIM may occur separately or in combination (CINM or CINMA) in patients presenting with generalized limb weakness as well as difficulty in weaning from the ventilator.

The relative frequency of CIM and CIP remains undefined, but it is accepted that many, if not most, patients have electrophysiologic and morphologic evidence of both, and with the associated medical risk factors, the incidence may reach 50% of those ICU patients. Although the predominance of either CIP or CIM may be dependent on the individual patient, previous use of neuromuscular blocking agents or corticosteroids were suggested as playing a role, but recently this has been challenged on epidemiologic data. However, in an ICU setting where these medications are often used in posttransplant patients, the incidence of CIM was high, whereas in another ICU where there were no posttransplant patients, and neuromuscular blocking agents or corticosteroids were rarely used, the incidence of CIM was low. The range of severity of combined CIP and CIM may be marked. Although CIN has also been reported in children, the reported incidence is considerably less than in adults, but may reflect poor case identification as well as a much lower incidence of SIRS in the pediatric ICU population.

For purposes of clarity the discussion of CIN and CIM are separated, but for the practicing clinician their approach to the weak, critically ill patient should begin with the assumption their patient may have CINMA. This approach is the most prudent as it keeps the evaluating clinician vigilant in identifying features of myopathy and polyneuropathy, which can have important implications in terms of prognosis.
CRITICAL ILLNESS POLYNEUROPATHY: CAUSE

In 1996, Bolton proposed that the axonal degeneration in CIN may be caused by factors attributed to sepsis, and the humoral response triggered by epithelial cells, endothelial cells, macrophages and neutrophils by inducing proinflammatory cytokines such as interleukins-1, -2, and -6, tumor necrosis factor (TNF)-α and free radicals. These humoral and cellular responses are activated in SIRS or sepsis, produce diffuse microcirculatory dysfunction throughout the body, and result in disturbances that impair energy substrate delivery to end organs, thereby causing organ dysfunction or failure. Although the exact pathophysiology of CIN remains unknown, it is thought that these pathways likely play a major role in the distal axonal degeneration of sensory and motor fibers that characterize this syndrome, but the specific process and extent may vary as can its effect on the metabolic or bioenergetic properties of nerve and muscle. The role of a neurotoxin in CIN has also been suggested, but is as yet unproved.

Although sepsis may be the only underlying factor in some patients, CIN has also been described in patients with anoxic coma after cardiac arrest, metabolic crises, or severe burns. CIN has also been associated with other conditions including prolonged mechanical ventilation, malnutrition, vitamin deficiencies, immunologic disorder, Guillain-Barré syndrome, toxin-producing bacteria, coagulopathies, use of gentamicin, neuromuscular blocking agents (pancuronium bromide), hyperosmolality or changes in osmolality, and hypotension. CIN is not limited to an ICU setting as patients with end-stage renal failure may develop a severe and rapidly developing axonal, predominantly motor polyneuropathy. Similarly, patients with chronic liver disease may have a mild, predominantly demyelinating motor and sensory polyneuropathy, but the SIRS occurring in this setting may rarely contribute to CIN development.

There does seem to be clear risk factors associated with CINMA and a recent systematic review of the literature identified hyperglycemia, SIRS, sepsis, MODS, renal replacement therapy, and catecholamine administration as the most probable. Despite the previously reported associations of CINMA with patient age, gender, severity of illness as well as use of glucocorticoids, aminoglycosides, and midazolam, this same review found no consistent relationship with its development.

CRITICAL ILLNESS POLYNEUROPATHY: CLINICAL MANIFESTATIONS

The clinical examination of a critically ill patient is limited by the environment in which it is undertaken and the ability of the patient to cooperate, because CIP is often preceded by an encephalopathy secondary to sepsis. In the setting of the ICU or a critically ill patient who has developed distal weakness or failure to successfully wean from mechanical ventilation, CIN is likely, but so is CIM, either separately or concurrently and the examination needs to be directed to either possibility; neuromuscular clinical manifestations may be occult in 50% of cases. Findings on physical examination include intact cranial nerve function and any abnormalities are exceedingly rare and should suggest an alternative diagnosis. Diffuse muscular atrophy, flaccid quadriparesis, and reduced to absent muscle stretch reflexes are identified, but muscle stretch reflexes may be normal in one-third of patients with CIN, or even hyperactive in those patients with associated central nervous system (CNS) lesions. Sensory testing is often unreliable in encephalopathic patients, but evidence of distal loss to pain, temperature, and vibration may be observed among more responsive patients.
CRITICAL ILLNESS POLYNEUROPATHY: ELECTRODIAGNOSTIC FEATURES

Electrodiagnosis is a critical part of the evaluation of the patient suspected of having CIN. The electrodiagnostic study itself should consist of upper and lower limb motor and sensory nerve conduction studies (NCS) and phrenic NCS performed when respiratory muscle failure is suspected. Repetitive nerve stimulation is helpful in excluding preexisting neuromuscular junction disorder or when weakness could be attributed to the administration of neuromuscular junction blocking agents. In CIN the motor CMAP amplitudes and sensory nerve action potential (SNAP) amplitudes are typically reduced, with normal or near normal conduction velocities and distal latencies. Decline in the CMAP amplitudes occurs early in the course of the illness, and may be followed by subsequent decline in the SNAP amplitudes. Features suggestive of demyelination such as significant conduction velocity slowing, prolonged distal latencies, temporal dispersion, or conduction block are typically not seen. However, prolonged CMAP durations, not accompanied by dispersion between proximal and distal sites of stimulation, when present, may be diagnostic of CIM. Needle electromyography (EMG) typically shows abnormal spontaneous activity in distal muscles, and may show reduced recruitment of motor unit potentials. The presence of small motor unit potentials on needle EMG should alert the electromyographer to the possibility of a concomitant myopathy, particularly if the SNAP amplitudes are normal or near normal.

CRITICAL ILLNESS POLYNEUROPATHY: PATHOLOGY AND PATHOPHYSIOLOGY

Nerve biopsy studies show axon loss and primary axonal degeneration with no evidence of inflammation, and predominant involvement of distal nerve segments. Peripheral axonal degeneration is associated with central chromatolysis of the anterior horn cells, as well as moderate loss of dorsal root ganglion cells. Axonal degeneration of intercostal and phrenic nerves and denervation atrophy in respiratory muscles may help to explain the respiratory insufficiency found in these patients.

There is also a correlation between serum concentrations of endotoxin and interleukin-2 receptors (IL2-R) and amplitude reduction of the compound motor action potentials. This finding apparently indicates that endotoxin damages nerve axons directly or indirectly, for example, by activation of inflammatory cascades (IL2-R). Endotoxin seems to be an essential factor in the pathogenesis of CIP in sepsis, and therapeutic options which neutralize endotoxin may prevent development of CIP.

CRITICAL ILLNESS MYOPATHY: CLINICAL MANIFESTATIONS

Similar to CIN, CIM is typically suspected following recovery from sedation and encephalopathy when patients exhibit difficulty weaning from mechanical ventilation. The predominant clinical feature of CIM is diffuse flaccid weakness involving all limb muscles, neck flexors, and frequently the facial muscles and diaphragm. Deep tendon reflexes may be decreased, and if elicitable, the sensory examination may be normal. Unlike inflammatory myopathies, myalgias are less commonly seen in CIM. Examination can again be challenging in encephalopathic patients or those who have received neuromuscular blocking agents.

Lacomis and colleagues have proposed various entities associated with pure muscle weakness in CIM and recognized 3 main subtypes:

1. **Thick filament myopathy**: primarily encountered in patients with severe asthma requiring ventilator support, high-dose corticosteroid, or neuromuscular blocking
Fig. 1. Presumed pathophysiologic mechanisms and other interactions involved in the development of CIP/CIM. ROS, reactive oxygen species; SR, sarcoplasmic reticulum. (From Hermans G, De Jonghe B, Bruyninckx F, et al. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev 2009;1:CD006832; doi: 10.1002/14651858.CD006832.pub2; with permission.)
agent use. Serum creatine kinase (CK) levels are mildly increased. Muscle biopsy reveals absence of thick myosin filaments.

2. *Acute necrotizing myopathy*: having multiple causes that all result in myoglobinuria; serum CK levels are markedly increased. Electrophysiologic studies show findings consistent with a severe myopathy. Muscle biopsies show widespread necrosis of muscle fibers.

3. *Cachectic myopathy*: also known as disuse atrophy and presents with marked wasting and weakness of muscles, but this remains a diagnosis of exclusion. Laboratory studies are generally nonspecific. Muscle biopsy may show type 2 fiber atrophy.

**CRITICAL ILLNESS MYOPATHY: ELECTRODIAGNOSTIC FEATURES**

Electrodiagnostic studies in critical illness myopathy most commonly reveal NCS with low amplitude CMAPs, with preserved conduction velocities and distal latencies. One specific feature may be a prolonged CMAP duration that does not show any dispersion between proximal and distal sites of stimulation.\(^3\) The actual CMAP duration may be normal or only mildly prolonged early in the patient’s illness, become prolonged later in the course of the illness, and subsequently shorten with recovery, but recognition of this pattern can help facilitate the diagnosis of CIM.\(^2\) SNAP amplitudes are typically preserved; however, low SNAP amplitudes can be seen in patients who have concomitant CIN or preexisting disease such as diabetic neuropathy, or decreased because of technical factors such as limb edema. Needle EMG reveals abnormal spontaneous activity, including fibrillation potentials and positive sharp waves. Rapid recruitment of small motor unit potentials is typically seen with voluntary activation. Electrodiagnostic studies can be challenging in patients who are sedated, encephalopathic, or profoundly weak, and determining whether a patient has CIM or CIP can be difficult in those situations. In such patients, the presence of reduced CMAP amplitudes, prolonged CMAP durations, and preserved SNAPs are most suggestive of CIM. The technique of direct muscle stimulation (DMS) can be of benefit in distinguishing weakness from CIN versus CIM because a higher amplitude motor response is recorded from nerve versus direct muscle stimulation and their ratio, nerve/muscle response amplitude, is greater than 0.5 with myopathy.\(^3\) However, DMS may have limited usefulness in mildly affected patients and a higher ratio may not distinguish between abnormal and normal muscle. The underlying pathophysiology for the abnormalities noted in DMS is believed to result from abnormal sodium channel inactivation in critical illness myopathy\(^3\) and a similar pathophysiology may explain the prolonged CMAP duration in CIM.\(^3\)

**CRITICAL ILLNESS MYOPATHY: PATHOLOGY AND PATHOPHYSIOLOGY**

Muscle biopsy findings are variable in patients who have critical illness myopathy and may demonstrate acute and chronic denervation as well as myopathic changes.\(^3\) Thick filament myosin loss seen on light and electron microscopy has been the most frequently reported pathologic finding in CIM.\(^3\) Atrophy is typically seen in type 2 fibers, but may involve type 1 fibers and necrosis is usually absent as are inflammatory changes.\(^3\)

Muscle necrosis has been reported in those patients with an acute necrotizing myopathy that clinically manifests with severe quadriplegia, marked increase in CK, and myoglobinuria.\(^4\)

The risk factors for CIM are similar to those of CIN. High-dose corticosteroids, non-depolarizing neuromuscular blocking agents, and sedating agents such as propofol\(^4\)
are also implicated as risk factors for its development, but CIM has also been reported in patients who have not been exposed,\(^{16,32,45}\) suggesting, as implied in a separate review, that they may not be as strongly linked as once believed.\(^{10}\) These underlying risk factors as well as muscle inactivity from various reasons may all contribute to the pathogenesis of CIM.\(^{37}\)

The pathophysiology of muscle dysfunction in CIM is as complicated as CIN. It includes functional changes in muscle membrane excitability with dysregulation of sodium channel gating causing inexcitability of skeletal muscle.\(^{46–48}\) Structural changes occur, such as myosin loss, and the proteolytic cascade involved in the breakdown of myosin and other muscle proteins, such as titin, nebulin, and actin, seems up-regulated.\(^ {37}\) This may reflect altered calcium homeostasis and suggested by the increased expression of calpain, a calcium-activated protease in atrophic muscle fibers.\(^ {38}\) However, any comprehensive explanation of the pathogenesis of CIM needs to include altered gene expression, disordered muscle membrane function, and proteolytic pathways involved in muscle protein breakdown (see Fig. 1).

**COMBINED CRITICAL ILLNESS POLYNEUROPATHY AND MYOPATHY: CINM OR CINMA**

Increasingly it is recognized that weakness in the critically ill patient is more likely to present with features of both polyneuropathy and myopathy on electrodiagnostic testing and muscle biopsy then a syndrome of either CIN or CIM.\(^ {49,50}\) The role of neuromuscular blocking agents and steroids remains unclear, but it is suggested that when not used, features of a polyneuropathy may predominate; in patients exposed to these drugs, a myopathy may be more prominent.\(^ {4,8,51}\) The coexistence, but varying prominence of nerve or muscle involvement has also been found in muscle biopsies in which myopathic features in addition to chronic denervation were identified.\(^ {3,10,52}\) Although some controversy exists in the literature with regard to the relative frequency of polyneuropathy or myopathy in the critically ill, but weak patient, the existence of an acute axonal motor variant of Guillain-Barré syndrome (GBS) also enters the differential diagnosis.\(^ {12}\) However, ancillary studies can assist in their differentiation. Findings favoring the diagnosis of CIN include normal CSF protein levels, electrophysiologic findings of axonal neuropathy, and nerve biopsy showing absence of inflammatory changes.\(^ {8,53}\) The axonal variant of GBS also characteristically occurs before presentation to the ICU setting, and is often associated with *Campylobacter jejuni* infection.\(^ {54}\)

**STEPWISE APPROACH TO THE MANAGEMENT OF SUSPECTED CRITICAL ILLNESS NEUROMUSCULAR ABNORMALITIES (CINMA)**

In critically ill patients presenting with weakness, regardless of whether they have been intubated, received neuromuscular blocking agents, or have a superimposed encephalopathy, require a detailed neurologic examination to exclude CINMA and preferably once sedation has been discontinued. Identification and characterization of a polyneuropathy or myopathy requires a comprehensive neurologic examination, electrophysiologic studies, and determination of serum creatine kinase levels. Diagnostic criteria to assist with an initial classification as a probable CIN and CIM have been outlined by Bolton.\(^ {55}\) The authors propose the following stepwise approach to the management of a patient diagnosed with a CINMA.

**Step 1: Recognize Neuroanatomical Localization of Weakness in the ICU Setting**

The approach should be systematic and localization based, considering possible involvement of the brain, spinal cord, peripheral nerves, muscle, or neuromuscular junction (Fig. 2). Neuromuscular conditions, such as motor neuron disease,
Fig. 2. Systematized approach to evaluation based on localization and causes.
myasthenia gravis, Lambert-Eaton myasthenic syndrome, or Guillain-Barré syndrome, can lead to respiratory failure and pneumonia caused by aspiration, particularly when the respiratory and bulbar muscles are involved. Rapidly progressive acute and subacute infectious or neoplastic disorders, causing myelopathy or polyradiculopathy, also need to be considered.

**Step 2: Identification of Pre- and Post-admission Conditions as Causation**

The past medical and family history needs to be carefully reviewed to identify the presence of a neurologic condition that may have preceded the development of the acute illness. Acute infective, traumatic, or neoplastic spinal cord compression, motor neuron disease, Guillain-Barré syndrome, myasthenia gravis, Lambert-Eaton myasthenic syndrome, muscular dystrophy are usually identified before the patient is placed on a ventilator.

The next consideration is those patients in the ICU for a variety of primary illnesses or injury, who develop SIRS and then, after a period of days or weeks, are observed to have difficulty in weaning from the ventilator. An underlying neuromuscular condition may be suspected if, after lung or cardiac causes of respiratory insufficiency have been eliminated, on attempted weaning their voluntary respirations are rapid, shallow, and accompanied by an increasing arterial blood [CO₂]. Clinical signs of neuropathy or myopathy in the limbs may not be present or clearly identified at this early stage. The potential occurrence of a cervical spinal cord injury needs to enter the differential as well as peripheral nerve, neuromuscular junction, or muscle dysfunction, when quadriplegia is present and requiring systematic investigation. Depending on the clinical presentation it may be necessary to consider magnetic resonance imaging (MRI) of the cervical spinal cord.

de Letter and colleagues have shown that assessment of Apache III, a quantitative index of disease severity, and the presence of the SIRS (severe sepsis), both predicted the later development of CIN and CIM.

**Step 3: Laboratory Evaluation of CINM**

The presence of focal signs on neurologic examination, such as hemiparesis, asymmetric hyperreflexia, or Babinski signs, should prompt further diagnostic testing; head CT or brain MRI, and CSF testing. Spinal cord imaging with either CT or MRI can also be considered for the critically ill patient who has weakness and upper motor neuron signs, such as hyperreflexia and Babinski signs, on examination. Although any further testing has to take into consideration the likelihood of a nonneuromuscular origin of the patient’s weakness, patient stability, and the risk of transportation of an acutely ill patient have to be incorporated into and may limit the extent of diagnostic testing that can be performed.

Electrodiagnostic testing, including NCS, needle EMG, and repetitive nerve stimulation (RNS), provides the best opportunity to characterize the cause of weakness as a disorder of anterior horn cells, peripheral nerve, muscle, or neuromuscular junction. Phrenic nerve conduction studies and needle EMG of the diaphragm may also assist in establishing CIP as the possible cause of failure to wean from the ventilator.

Serum CK determination and muscle biopsy are occasionally used to characterize the nature of a suspected myopathy. Markedly increased CK levels suggest a necrotizing myopathy, whereas in other types of CIM, serum CK increases are not as increased. In CIP, serum CK levels are either normal or only mildly increased. Muscle biopsy is occasionally indicated to differentiate critical illness myopathy from other myopathies or from critical illness polyneuropathy and may be necessary to guide treatment as well as prognostication.
Step 4: Pharmacologic and Nonpharmacologic Management

General treatment
A multidisciplinary approach must be used in managing a patient with CINMA, but focused on treating the underlying critical illness. Prevention of decubitus ulcers, prophylaxis of deep vein thrombosis, and aggressive physical therapy are mandatory. Because corticosteroids and neuromuscular blocking agents may be important in the pathogenesis, these agents should be avoided if at all possible. Clearly the continued aggressive treatment of infection, hypotension, and hypoxemia is vital as is ongoing treatment of organ failure.

Management of CIN
Despite aggressive treatment of underlying sepsis, organ failure, and ventilatory support, the mortality in sepsis and multiple organ failure in the ICU is still approximately 30% to 50%. However, with early institution of proper and aggressive treatment of the acute illness, CIN often improves in a matter of weeks in mild cases, or months if severe, but when severe, recovery may not occur. Administration of intravenous immunoglobulin (IVIgG) has been attempted, but without significant benefit. There is now substantial evidence that intensive insulin therapy reduces the incidence of CIN/CIM, decreases the duration of mechanical ventilation, ICU stay and 180-day mortality. However, there is the risk of hypoglycemia and associated neurologic complications.

Avoidance of drugs that may further perpetuate injury is obviously warranted. Physical therapy and rehabilitation may be helpful in accelerating recovery, but as yet there is a lack of rigorous evidence to support that practice.

Management of CIM
Because corticosteroids and neuromuscular blocking agents may contribute to CIM, they are best avoided or used in the lowest possible dosages or only for the briefest period of time. Muscle biopsy should be considered if another myopathic process, such as an inflammatory myopathy, is suspected and the histologic findings would affect management. Severe CIP and necrotizing myopathy may have a poor prognosis for motor recovery, but the prognosis is better for rhabdomyolysis, cachectic myopathy, and thick filament myosin loss, and such prognostic information could be obtained from a muscle biopsy.

Specific treatment
Specific treatments for CIN and CIM are mainly supportive and symptomatic. However, the following general comments concerning the specific organ systems or theoretically interesting interventions are addressed:

1. Neurologic. Frequent neurologic assessments are required to document status and unexpected new neurologic developments.
3. Respiratory. Respiratory therapy is important in minimizing the risk of a new pulmonary infection.
4. Dermatologic. Skin protection measures should be initiated, with an appropriate mattress to optimize pressure relief and frequent turning of the patient to prevent the development of pressure ulcers.
5. Endocrine. Intensive insulin therapy to address hyperglycemia remains the best specific treatment to reduce the incidence of ICU-acquired neuromuscular disorders, but carries an increased risk of hypoglycemia. The rate of CINM defined...
by electrodiagnostic testing was reduced from half to one-third when serum glucose was maintained between 80 and 110 mg/dL, compared with a conventional glucose goal of 180 to 200 mg/dL. Intensive insulin therapy also has an anti-inflammatory effect by lowering circulating levels of ICAM and E-selectin levels, improves deranged lipid profile, decreases plasma NO by reducing inducible nitric oxide synthase expression, which then results in protection of the endothelium in critically ill patients.30,51 Unfortunately, polyneuropathy was not a reported end point in the investigation of intensive insulin therapy in medical ICU patients.69 In addition, there was no significant difference in duration of ICU stay, hospital stay, mortality, duration of mechanical ventilation or need for prolonged mechanical ventilation in the studied sample.70 The use of testosterone derivates69 and growth hormone has not been successful in improving neuromuscular function or decreasing the length of ventilation.71

6. **Immunologic.** Have included the use of monoclonal and polyclonal antibodies directed against bacterial endotoxin; tumor necrosis factor (TNF) alpha; soluble TNF receptors; interleukin-1 receptor antagonists71; N-acetylcysteine, a drug that acts as an oxygen radical scavenger72; and various hemofiltration techniques and plasma exchange.12,73–75 Treatment of CIN with intravenous immunoglobulins (IVIG) has been used as a supplemental treatment of sepsis in critically ill patients in whom it showed some promise in reducing the morbidity associated with sepsis. Wijdicks and Fulgham63 failed to show improvement in CIP, but, in a more extensive study,75 early treatment of gram-negative sepsis with IVIG may have prevented the development of CIP. Experience from another series of patients suggests that IVIG may reduce the likelihood of developing CIN.75 The finding of reduced levels of activated protein C in sepsis, which promotes intravascular thrombosis, was increased by the administration of recombinant human activated protein C and accompanied by a significant reduction of morbidity and mortality,29 but whether this treatment is beneficial in CIP requires further investigation.

7. **Infectious disease.** Initial treatment approach involves the prevention and management of sepsis, SIRS, and multiple organ dysfunctions.

8. **Nutritional:** The role of specific parenteral and enteral nutrition is controversial. Some have theorized that these procedures may induce alteration in the metabolism of fats and glucose, which would have deleterious effects on peripheral nerve.70,76,77 However, studies have shown no statistical relationship between the administration of enteral or parenteral nutrition and the development of CIN77–79 and include nutritional schemes or interventions,20 supplement therapies,80 antioxidant therapy.81 Dysfunction of the gut may be prevented by early use of enteral feedings.

9. **Rehabilitation.** Involvement of physiatry is ideally initiated immediately following the recognition of neuromuscular disease in the ICU. Initially, only light exercises to promote muscle strength, maintain joint mobility, and prevent contracture should be instituted. As the patient improves, progressive strengthening of the major upper and lower extremity muscle groups is followed by training in activities of daily living. The program of rehabilitation may be lengthy and require the use of a variety of assistive devices.64,65,82,83 As the patient improves, therapy can be advanced, with gradual mobilization. Most patients benefit from transitioning to an inpatient rehabilitation unit once clinically stable, with the goal of returning home to independent living. Disposition at discharge is influenced by the functional deficits at the time of admission to the acute rehabilitation unit, underlying pathophysiology of the disease process and associated rate of recovery, and
the degree of social support available at home. Although controlled studies are lacking, whole body vibration training has been used in a multitude of conditions as a means of muscle strengthening, improving balance as well as increasing bone mass.⁸⁴,⁸⁵

10. **Speech and swallowing.** Speech and swallowing needs to be assessed in a patient with an extended ICU stay. Appropriate interventions are required to manage significant facial weakness that could contribute to dysarthria or dysphagia.

11. **Renal.** Fluid resuscitation, the use of inotropics, and diuretic drugs, in various combinations, may prevent renal failure.

12. **Neuropsychology.** As mentioned earlier a multidisciplinary approach is required for overall success in the management of these patients. It remains essential for other team members such as a neuropsychologist and recreational therapist to optimally maximize the patient’s chance of returning to the premorbid level of function as quickly as possible.

**Step 5: Discussion of Prognosis with the Patient and Family**

Prognosis depends on the extent of axonal or muscle damage, yet full recovery often occurs in mild to moderate cases, but in severe cases, recovery may be longer or incomplete and associated with a higher mortality.³,⁶,⁷ In CIP, with distal axonal degeneration, recovery depends on the distance over which regeneration occurs; the greater that distance the longer the recovery time³,⁵ and the more incomplete the recovery.⁴,⁷,⁹,⁸³ Clinical and neurophysiologic evidence of neuropathy may remain for up to 5 years after ICU discharge¹¹ and patients with severe CIP may remain quadriplegic.⁷⁹

In patients who have a predominantly myopathic process, absence of necrosis on muscle biopsy, and lack of serum CK increase are favorable findings even in cases with profound weakness.⁴ Patients who have high serum CK increases and necrosis on muscle biopsy have a less favorable prognosis.⁸⁶ Weakness in CIM can develop rapidly, but although recovery can also be as rapid, complete recovery may be prolonged. With severe CIM paralysis there is also greater muscle protein loss, and regaining ambulation after CIM in these situations may take several months.⁸⁷

The risk of myopathy is largely determined by the severity and duration of the underlying illness, whether it is a sepsis syndrome or status asthmaticus. Nearly total muscle inactivity contributes to the myopathy so it may be possible to alleviate some degree of the risk of muscle injury by permitting as much muscle activity as can be done safely. In one study that mandated withdrawal of sedatives to determine their ongoing need, avoided over sedation and total time of mechanical ventilation was shortened without increasing the risk of complications.⁸⁷ Despite these measures, the mortality in sepsis and multiple organ failure in the ICU remains as high as 30% to 50%.⁷¹,⁸⁸ Nonetheless, with institution of treatment, CIN and CIM can improve in a matter of weeks in mild cases and months in severe cases.⁷⁹,⁸⁹–⁹²

**SUMMARY**

CIP and CIM are among the most common neuromuscular complications in critically ill patients and can be collectively conceptualized as CINMA. Signs and symptoms of CINMA must be recognized early so proper measures are taken to help ensure the best possible recovery after sepsis or MODS. Patients are typically diagnosed when they fail to wean from ventilatory support (despite adequate cardiopulmonary status), or when severe limb weakness is noted during or following recovery from critical illness. Exploration of the past medical history is necessary to exclude preexisting
neuromuscular conditions and electrodiagnostic testing helps to establish the diagnosis. NCS in CIN and CIM show low amplitude CMAPs, whereas reduction in SNAP amplitudes would be expected only in CIN. Needle EMG in both conditions can show abnormal spontaneous activity; however, in CIN large motor unit potentials with reduced recruitment are encountered although in CIM small motor unit potentials with rapid recruitment would be expected. Pathogenesis of critical illness polyneuropathy and myopathy remains tentative, and the roles of corticosteroids and neuromuscular blocking continue to be delineated.

Treatment consists of avoidance of potentially harmful agents, and although otherwise supportive, intensive insulin therapy has currently been shown to lower the risk of CINMA development. Future therapeutic interventions will require better understanding of disease pathogenesis, but may target proinflammatory cytokine and free-radical pathways, muscle gene expression, ion channel function, or proteolytic muscle protein mechanisms. Rehabilitation is initially targeted at maintenance of range of motion and prevention of contractures, with progression to gradual mobilization and submaximal strengthening as clinically indicated, and provision of adaptive equipment, to maximize functional independence. Prognosis depends on the extent of the underlying muscle and nerve damage. In general, recovery is prolonged and often incomplete in patients who have severe axonal damage and quadriplegic myopathy with increased serum CK level and necrosis on muscle biopsy.

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