Electrophysiology of Neuromuscular Disorders in Critical Illness

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EDUCATIONAL OBJECTIVES  Upon completion of this monograph, the reader will acquire skills to: (1) summarize neuromuscular causes of weakness in intensive care unit (ICU) patients, (2) describe electrophysiologic characteristics and findings in diagnosis of neuromuscular disorders in critically ill ICU patients, (3) explain the pathophysiology of critical illness myopathy and critical illness neuropathy and how electrodiagnostic studies can help to diagnose and differentiate these disorders, and (4) develop a differential diagnosis of weakness in the ICU, know what tests should be done to arrive at the correct diagnosis and understand basic management principals.

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ELECTROPHYSIOLOGY OF NEUROMUSCULAR DISORDERS IN CRITICAL ILLNESS

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ABSTRACT: Introduction: Neuromuscular disorders, predominantly critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) occur in approximately one-third of patients in intensive care units. The aim of this study was to review the important role of electrophysiology in this setting. Results: In CIM, sarcolemmal inexcitability causes low amplitude compound muscle action potentials (CMAPs) that may have prolonged durations. Needle electrode examination usually reveals early recruitment of short duration motor unit potentials, often with fibrillation potentials. In CIP, the findings are usually those of a generalized axonal sensorimotor polyneuropathy. Direct muscle stimulation aids in differentiating CIP and CIM and in identifying disorders along with other electrophysiologic and histopathologic studies. Identifying evolving reductions in fibular CMAP amplitudes in intensive care unit (ICU) patients predicts development of neuromuscular weakness. Conclusions: Knowledge of the various neuromuscular disorders in critically ill patients, their risk factors, and associated electrodiagnostic findings can lead to development of a rational approach to diagnosis of the cause of neuromuscular weakness in ICU patients.

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HISTORY

Development of modern intensive care units (ICUs) and other medical advances has led to increased survival of critically ill patients. By the late 1970s, it became apparent that many survivors acquired neuromuscular disorders that differed from Guillain-Barré syndrome (GBS) or other “traditional” neuromuscular disorders that result in ICU admission. Bolton and colleagues were the first to report the results of routine electrophysiologic testing in patients who acquired neuromuscular disorders while in the ICU. Their work produced the first comprehensive descriptions of critical illness polyneuropathy (CIP) and created a new field of medicine, the study of neuromuscular disorders associated with critical illness.1–5

Because the vast majority of critically ill patients with neuromuscular disorders are evaluated in the ICU, it is appropriate to begin this review with discussion of aspects of electrodiagnostic testing performed in that setting.

ELECTRODIAGNOSTIC (EDX) STUDIES IN THE ICU: INDICATIONS AND DIFFICULTIES

The most common indications for performing an EDX study in the ICU are weakness and ventilatory failure. Occasionally, patients are evaluated for mononeuropathies or plexopathies that occur perioperatively or in the ICU, often from iatrogenic causes. The approach to these conditions is no different than in noncritically ill patients.6,7 With regard to the generalized neuromuscular disorders, the weakness is usually diffuse and at least moderately severe to warrant an EDX study. The majority of causes of generalized neuromuscular weakness encountered in the ICU are listed in Table 1.8–18 Some are acquired during critical illness, and the others cause critical illness and precipitate ICU admission. Those disorders which also cause ventilatory failure are noted in Table 1. Isolated phrenic nerve injuries and cervical spinal cord lesions can also cause ventilatory failure. This review will mainly consider the disorders acquired during critical illness, but features that allow differentiation from the other conditions will be addressed.

EDX Testing in the Intensive Care Unit. Performing an EDX study in the ICU can be a daunting task. The environment is electrically unfriendly, and 60 cycle artifact is routinely encountered, especially on sensory nerve conduction studies (NCS), F-wave testing, and needle electromyography. To reduce this interference, lights and unnecessary electrical equipment should be turned off, and the electromyography (EMG) machine should be plugged into a separate outlet. A notch filter may also lessen 60 cycle artifact, but these maneuvers may not remove it. Fortunately, fibrillation potentials and other abnormal spontaneous discharges, when present, can be heard easily even if they cannot be seen. Increasing the low-frequency filter can also allow abnormal spontaneous activity to be visualized in this situation (Fig. 1).

ABBREVIATIONS: CIM, critical illness myopathy; CIP, critical illness polyneuropathy; CK, creatine kinase; CMAPs, compound muscle action potentials; CSF, cerebrospinal fluid; dCMAP, direct muscle stimulated CMAP; DMS, direct muscle stimulation; EDX, electrophysiologic; EMG, electromyography; GBS, Guillain-Barré syndrome; ICU, intensive care unit; IVCS, intravenous corticosteroids; MFOVs, muscle fiber conduction velocities; MUAPs, motor unit action potentials; NCS, nerve conduction studies; neCMAP, nerve evoked CMAP; SIRS, systemic inflammatory response syndrome; SNAP, sensory nerve action potential

Key words: critical illness myopathy; critical illness polyneuropathy; intensive care unit; myopathy; neuromuscular disorders; polyneuropathy

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Another problem is that patients are often cool, and warming is more difficult; it can be performed with heat packs and sometimes a warming blanket. Edema at recording sites can be a more significant problem that must be taken into account when interpreting the significance of a low amplitude sensory nerve action potential (SNAP). Finding a sufficient number of routine recording and stimulation sites for NCS may also be difficult due to the presence of intravenous and intra-arterial cannulations.

EDX physicians should also pay even more attention to electrical safety in the ICU and avoid stimulating in regions of fluid spills, especially if they are adjacent to subclavian or jugular catheters so that a cardiac arrhythmia is not induced. Patients with external pacemakers should not undergo NCS.19

NEUROMUSCULAR DISORDERS ASSOCIATED WITH CRITICAL ILLNESS: EPIDEMIOLOGY AND CLINICAL FEATURES

The conditions most commonly encountered are critical illness myopathy (CIM), CIP, and a combination of these disorders. Prolonged neuromuscular junction blockade is seen very rarely now. It was more frequently encountered, although never commonly, when continuous infusions or high intermittent doses of paralytics were administered routinely.20–25

It is rare for preexisting subclinical neuromuscular disorders to become manifest in a critical illness state either as a consequence of treatment or due to the stress of illness. For example, neuromuscular junction disorders, especially myasthenia gravis, could be precipitated or worsened by use of magnesium or aminoglycosides. Occasionally, GBS occurs postoperatively or after a serious viral illness for which the patient was already in the ICU. Wound botulism can also occur in the ICU, but it is extremely rare. Occasionally, disorders that are typically diagnosed before ICU admission, such as amyotrophic lateral sclerosis, are first diagnosed in the ICU when they manifest as ventilatory failure or airway collapse. These disorders are listed in Table 1.

Prospective Studies of Neuromuscular Weakness in Critical Illness. Prospective studies of patients admitted to ICUs for various reasons, especially sepsis, the systemic inflammatory response syndrome (SIRS),26,27 or multi-organ failure with or without acute lung injury, show that 25% to 40% developed clinical evidence of a neuromuscular disorder28–34 (Table 2). EDX evidence of a neuromuscular disorder occurs in up to 90%.28 Many of the patients reported in these studies had mixtures of CIP and CIM. In these combined studies, there was often not a clear-cut association between the development of neuromuscular weakness and medications or sepsis. However, most studies that address CIP and CIM separately and comprehensively provide a somewhat different message that is discussed below.4,5,35–44 Children as well as adults may be affected, but there are no prospective studies of childhood onset CIP or CIM.

Critical Illness Polyneuropathy. Prospective studies of patients admitted to the ICU primarily for sepsis and multi-organ failure reveal that 47 to 70% develop at least EDX evidence of an axonal sensorimotor polyneuropathy, usually within 1–3 weeks.4,5,35–41 (Table 2). Of these, 35–50% have substantial weakness. Sepsis or SIRS is considered to be the most important risk factor for developing CIP, and the severity and duration of illness as well

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** Fibrillation potentials in a patient with CIM. The top panel has marked 60 Hz artifact. In the bottom panel, the low frequency filter was increased from 20 to 500 Hz.

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*Table 1. Causes of neuromuscular weakness in ICU patients.*

<table>
<thead>
<tr>
<th>Disorders acquired in the ICU</th>
<th>Disorders that may lead to ICU admission</th>
<th>Disorders that rarely result in ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical illness myopathy</td>
<td>Guillain-Barré syndrome</td>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>Critical illness polyneuropathy</td>
<td>Myasthenic crisis</td>
<td>Inflammatory myopathy</td>
</tr>
<tr>
<td>Combined critical illness myopathy and polyneuropathy</td>
<td>Amyotrophic lateral sclerosis &amp; other motor neuron diseases</td>
<td>Acid maltase deficiency (Adult onset Pompe disease)</td>
</tr>
<tr>
<td>Rhabdomyolysis (from toxins, sepsis, etc.)</td>
<td>Botulism, including wound botulism</td>
<td>Hydroxychloroquine myopathy</td>
</tr>
<tr>
<td>Neuromuscular junction blockade</td>
<td>Lambert Eaton myasthenic syndrome</td>
<td>Vascular polyneuropathy</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Porphyria</td>
<td></td>
</tr>
</tbody>
</table>

*Arise rarely or are unmasked in the ICU.*
as hyperglycemia also appear to be risk factors.\textsuperscript{4,35,38–41} Hypoalbuminemia and nutritional factors may also play roles.\textsuperscript{4,37} Intensive treatment of hyperglycemia in the ICU is associated with a reduction in neuromuscular weakness and is discussed later.\textsuperscript{45–49}

The clinical features are generalized flaccid weakness, which is sometimes worse distally, ventilatory failure, hyporeflexia, or areflexia, and muscle atrophy. Distal sensory loss may be identified in the majority,\textsuperscript{5,50} but it is not always reported due to confounding factors such as encephalopathy, which is usually improving as CIP is recognized. Extraocular muscles are not affected. Cerebrospinal fluid is usually normal, but mildly elevated protein levels occur.\textsuperscript{3,50}

**Critical Illness Myopathy.** Compared with CIP, there are fewer prospective studies of CIM (Table 2). In patients with status asthmaticus and chronic obstructive pulmonary disease, the reported incidence is approximately 35%.\textsuperscript{42,44} In a study of patients with status asthmaticus, 76% developed elevations in serum creatine kinase (CK). In these studies, illness severity and use of intravenous corticosteroids (IVCS) were the major risk factors. In a prospective study of 100 patients undergoing liver transplantation, 7% developed severe weakness (less than anti-gravity power) due to CIM.\textsuperscript{43} Milder CIM could not be differentiated from weakness from underlying medical illness due to the study design, but severity of illness was a risk factor for CIM. All patients received IVCS and paralytics. In another study, CIM was diagnosed primarily based on the finding of reduced muscle membrane excitability and was noted in 22 of 40 patients within a week of ICU admission. The identified risk factors were systemic inflammation, disease severity, use of catecholamines, sedation requirements, and insulin growth factor binding protein 1, but not IV hydrocortisone for septic shock, paralytic agents, or aminoglycosides. This patient population did not receive high-dose corticosteroids. Muscle pathology was not examined.\textsuperscript{51}

Retrospective studies have generally considered IVCS to be a major risk factor along with paralytic agents. However, many cases did not have paralytic agent exposure, and some critically ill patients without exposure to either IVCS or paralytics develop CIM.\textsuperscript{52–54} On the other hand, SIRS is not a requirement for CIM.\textsuperscript{55} Thus, there is still controversy as to whether IVCS are a major risk factor for CIM, but it is fair to state that in studies that demonstrated loss of myosin thick filaments (also discussed later), the vast majority of patients received IVCS.

Patients with CIM have generalized flaccid weakness that is sometimes proximal-predominant, and they often have ventilatory failure. Facial weakness may occur, and extraocular muscle weakness has been reported rarely. Tendon reflexes may be normal or reduced, and sensation is normal\textsuperscript{42,43,55–60} As mentioned above, serum CK levels are often elevated transiently,\textsuperscript{42,55} but elevations are not always detected, especially if the level is assessed after 10 days or more of ICU treatment.\textsuperscript{37,58}

Patients with mixed CIM and CIP can have a combination of the features described above.

**Prolonged Neuromuscular Junction Blockade.** This syndrome is quite rare and is associated with prolonged use and high doses of paralytic agents, especially in patients with renal and sometimes liver failure. Vecuronium is the most commonly reported offending agent, but other neuromuscular junction blockers can cause this syndrome. Affected patients have generalized flaccid weakness

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**Table 2. Summary of prospective studies of neuromuscular weakness in the ICU.**

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Population</th>
<th>Incidence</th>
<th>Major risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>ICU &gt; 7 days</td>
<td>Up to 90% by EMG</td>
<td>Inconsistent results; often sepsis or multi-organ failure</td>
</tr>
<tr>
<td>CIP &amp; CIM</td>
<td>Sepsis</td>
<td>&gt;25% Weak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multi-organ failure</td>
<td>63–82% by EMG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute lung injury</td>
<td>21–41% Weak</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>57% by EMG</td>
<td></td>
</tr>
<tr>
<td>CIP</td>
<td>Sepsis/SIRS</td>
<td>28% Clinically</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>CIP</td>
<td>Prolonged mechanical ventilation</td>
<td>35–50% Weak</td>
<td>Sepsis; multi-organ failure; Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47–63%</td>
<td></td>
</tr>
<tr>
<td>CIM</td>
<td>Status asthmaticus;</td>
<td>35%; 76% inc CK</td>
<td>Illness severity; corticosteroid dose; renal failure</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease;</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver transplantation</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>
with ventilatory failure and hyporeflexia, usually with ophthalmoplegia. It is sometimes seen in conjunction with CIM or CIP.

**Other Neuromuscular Disorders in the ICU.** Disorders that more typically lead to ICU admission rather than occurring de novo in the ICU are listed in Table 1. Of these, the acute motor axonal neuropathy form of GBS could mimic CIP. It is relatively rare in North America and is usually associated with an antecedent diarrheal illness and *Campylobacter jejuni* infection. The cerebrospinal fluid (CSF) protein is usually substantially elevated in acute motor axonal neuropathy and not in CIP. The typical demyelinating form of GBS not only has an elevation in CSF protein, but also EDX features of a demyelinating polyneuropathy, especially prolongation of F-wave latencies and sometimes conduction block. Such findings are not seen in CIP.2

Neuromuscular junction disorders and motor neuron diseases could mimic CIM to some degree, and they may become manifest in the ICU due to the stress of illness or use of magnesium or aminoglycosides. Clinical features of myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), and botulism can overlap with CIM, and decreased compound muscle action potential (CMAP) amplitudes may occur. Decremental responses at low rates of repetitive stimulation are usually present in myasthenia and often in LEMS, while incremental responses with rapid rates of stimulation or following 10 seconds of exercise occur with LEMS and botulism.68 Repetitive stimulation is normal in CIM. Motor neuron diseases tend to be more asymmetric, and the presence of fasciculations is an important differentiating clinical feature. Poliomyelitis from viruses such as West-Nile have a CSF pleocytosis, and CIM does not. Low CMAP amplitudes are also common in motor neuron diseases as well as CIM (see next section), but the needle examination in motor neuron diseases should demonstrate fasciculation potentials and reduced recruitment of high amplitude long duration motor unit potentials (MUPs) in affected body regions.

Other inflammatory or toxic processes such as vasculitic polyneuropathy or inflammatory myopathy are rarely first diagnosed in the ICU, but they could have features that overlap with CIP and CIM. Tissue biopsies may be required to differentiate these conditions. Biopsies should be considered in patients more likely to have these inflammatory processes, such as those with connective tissue diseases, systemic vasculitides, asymmetric polyneuropathy, or in patients who are not improving following resolution of the critical illness.

Rhabdomyolysis, characterized by a highly elevated CK, can sometimes occur with other clinical features of CIM and muscle necrosis histologically. It can be considered to be part of the spectrum of CIM, while some may elect to consider it a different form of CIM. Nevertheless, such patients have substantial weakness and EMG findings of a necrotic myopathy, including fibrillation potentials. Rhabdomyolysis can also occur separately in the setting of critical illness due to medications and probably infection itself. Rather than having severe weakness and typical EDX findings of a necrotic myopathy, including fibrillation potentials, these patients tend to have myalgias, muscle swelling, and either a normal EMG or minimal EMG changes such as sparse fibrillation potentials.69

### Table 3. Summary of electrodiagnostic features in CIM and CIP.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>CMAP</th>
<th>SNAP</th>
<th>Direct muscle stimulation</th>
<th>Spontaneous activity</th>
<th>Motor unit potentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIM*</td>
<td>Low amplitude; +/- long duration</td>
<td>Normal</td>
<td>Low CMAP; CMAP to CMAP ratio of &gt;0.7</td>
<td>Fibrillation potentials in &gt;70%; May be diffuse</td>
<td>Short duration, low amplitude with early full recruitment</td>
</tr>
<tr>
<td>CIP*</td>
<td>Low amplitude</td>
<td>Low amplitude or absent</td>
<td>CMAP to CMAP ratio of &lt;0.5</td>
<td>Fibrillation potentials in all; 30% diaphragm fibrillation potentials</td>
<td>Decreased recruitment; evolving “neurogenic” morphology</td>
</tr>
</tbody>
</table>

*Absence of decremental response with repetitive stimulation and absence of conduction block or prolonged F-waves.

dmCMAP, direct muscle stimulated CMAP.

neCMAP, nerve evoked CMAP.

**EDX FINDINGS IN CIP AND CIM**

**CIM. Routine NCS.** On NCS, the most common finding is a reduction in CMAP amplitudes (Table 3). In biopsy-proven case series, >87% of patients have at least one low amplitude CMAP. Typically, more than 1 CMAP is low, and the reductions are usually more than 50% below the lower limit of normal.54,58,70,71 Bolton notes that phrenic CMAP amplitudes may also be low in CIM.21

In at least some patients, the CMAP duration is also increased substantially.72–74 (Fig. 2) This finding is probably under-recognized and may be common.73,74 It tends to be present in multiple nerves but to varying degrees, and it occurs due to...
slowing of muscle fiber conduction velocity and reduced excitability of the sarcolemmal membrane (see below).

It is difficult to determine when the EDX abnormalities begin in "pure" CIM, but they typically occur during the first 1–2 weeks of critical illness. In some studies of mixed CIM and CIP, earlier abnormalities were detected. For example, a study of 48 septic patients who underwent testing within 72 h of admission reported low CMAPs in 9 (19%) and either low CMAPs and SNAPs or only low SNAPs in 22 (28%). These abnormalities also had prognostic significance; 45% with abnormal NCS died compared to 0/17 with normal studies (P = 0.001). A total of 72% of patients had at least a 30% decline in CMAP amplitudes over 7 days, and this decline predicted neuromuscular weakness. In another series of CIM, CIP, and mixed CIM/CIP patients with multi-organ failure, NCS were first performed typically within 3 days, and this decline predicted neuromuscular weakness. In CIP, normal muscle excitability was maintained. In CIM, the ratio of neCMAP to dmCMAP is closer to 1 (both absent responses also equal 1), whereas in CIP, the ratio was <0.5. Other axonal nerve injuries simulate CIP on DMS, while periodic paralysis simulates CIM (Fig. 3).

Various muscles have been studied, especially the tibialis anterior. Others have modified the technique somewhat but report similar findings. For example, Trojaborg et al. used stimulating surface electrodes and surface subdermal or concentric needle electrodes for recording the dmCMAP, while Lefaucher et al. used a concentric needle electrode for recording. Seghelini has reviewed the topic and points out that there is sometimes a discrepancy between the results of direct muscle stimulation (DMS) and muscle histopathology.

Coexisting neuromuscular junction blockade also causes a reduction in CMAP amplitude, so an abnormal decrement should be sought with 2–3 Hz repetitive stimulation in appropriate patients. If LEMS or botulism is suspected, rapid rate repetitive stimulation should also be used if the patients are unable to exercise to test post-tetanic potentiation.

SNAPs are usually normal. If a low SNAP is present, it is usually attributed to coexisting neuropathy or a confounding problem such as edema at the recording site. A key feature in CIM is a reduction in CMAP amplitude that is far out of proportion to any reduction in the corresponding SNAP amplitude (e.g., a median CMAP amplitude of 1mV and a median SNAP amplitude of 10 μV).

**Direct Muscle Stimulation and Sarcolemmal Membrane Inexcitability.** Direct needle stimulation was first used to evaluate critically ill patients with weakness by Rich et al. after they postulated that loss of muscle membrane excitability accounted for the low CMAPs in CIM. They placed a 0.4 mm diameter subdermal needle electrode in the distal third of the muscle away from the end-plate region and an anode subdermal needle electrode 5 mm laterally. They used this stimulating pair to produce a recurrent twitch and then placed a recording subdermal needle electrode 1–3 mm proximally to get a maximum direct muscle stimulated CMAP (dmCMAP) using a surface electrode as a reference. Reduced excitability was demonstrated in CIM. They then compared the dmCMAP to the nerve-evoked CMAP (neCMAP). After obtaining the maximal dmCMAP, they used the same recording electrode pair and performed surface stimulation of the appropriate nerve; e.g., the fibular nerve when performing direct muscle stimulation of the tibialis anterior, and recorded the neCMAP. They then compared the peak-to-peak amplitude of the neCMAP to the amplitude of the dmCMAP. In CIP, normal muscle excitability was maintained. In CIM, the ratio of neCMAP to dmCMAP is closer to 1 (both absent responses also equal 1), whereas in CIP, the ratio was <0.5. Other axonal nerve injuries simulate CIP on DMS, while periodic paralysis simulates CIM (Fig. 3).

FIGURE 2. A: In a patient with CIM, the median CMAP has a very low amplitude and very prolonged duration. B: Normal median CMAP for comparison.
Allen et al. also examined excitability and conduction through muscle fibers. They used a monopolar stimulating electrode and concentric recording electrode to perform DMS of the tibialis anterior at low stimulus intensity. (See Fig. 4 for an example of the set-up for DMS.) They assessed dmCMAPs, calculated muscle fiber conduction velocities (MFCVs), and found slowing in CIM and an inverse correlation between slowing of conduction and CMAP duration. More severe CIM had slower MFCVs and longer CMAP durations (Fig. 5). They also assessed excitability using a paired stimulation technique. The absolute refractory period is the interstimulus interval at which the fiber identified becomes inexcitable to the second of the paired stimuli. Some fibers were completely inexcitable in CIM.

In addition, velocity recovery cycles of muscle action potentials have also been used for assessment of muscle membrane function in CIM. In 10 patients, velocity recovery cycles were recorded from the brachioradialis muscle by DMS, and it was found that muscle fibers were depolarized, likely because sodium channel inactivation was increased.81

Needle Electrode Examination. In prospective studies or pathologically-confirmed retrospective series, the needle examination reveals positive waves, fibrillation potentials, or both in at least 1 muscle in 71–100%.4,43,54,58,71 Usually, the abnormal spontaneous activity is noted diffusely and is of variable severity. There may not be a correlation between the amount of fibrillation potential activity and the degree of weakness.82 It is difficult to ascertain how early fibrillation potentials occur, but they have been reported in CIM patients within 7 days of stopping paralytics83 and within 11 days of liver transplant,84 so it is likely that they occur earlier than in denervating processes like CIP. With regard to other forms of abnormal insertional
or spontaneous activity, myotonic discharges are sometimes encountered locally. In MUPs are short in duration and low in amplitude with polyphasia in proximal and distal muscles (Fig. 6). Occasionally, proximal muscles are more severely affected. Recruitment may be difficult to assess in ICU patients when they are sedated, encephalopathic, or severely weak. MUPs may fire in short bursts. When it can be analyzed, recruitment is usually noted to be rapid or early.

Needle examination findings of the diaphragm have not been reported in CIM. Normal diaphragm MUPs usually have a confounding “myopathic” appearance and would likely be hard to distinguish from CIM-related MUP changes.

CIP. Routine NCS. The findings are those of an axonal polyneuropathy, namely reductions in amplitudes of both SNAPs and CMAPs without significant slowing of conduction velocities (Table 3). CMAP durations are not reportedly increased in CIP. The abnormalities are generally worse in the legs compared to the arms (length-dependent pattern). In some studies, CMAPs were more often affected, but CIM and neuromuscular junction blockade should be excluded in that setting. In fact, CIP is defined as a polyneuropathy that occurs in critically ill patients, presents with difficulty weaning from the ventilator and possible limb weakness, and has electrophysiologic evidence of motor and sensory axon loss. Phrenic CMAPs are also often reduced.

The NCS findings are generally present by day 13–14 of critical illness, and most improve over 2 months. Low amplitudes may be noted within a week and as early as 72 h after onset of sepsis as discussed above. In the study of patients with a mixture of CIP and CIM, early reductions in amplitudes were predictive of development of neuromuscular weakness and morbidity associated with sepsis. Leitjen et al. also reported that finding evidence of CIP on nerve conductions in ICU patients was predictive of mortality. The CRIMYN study, also discussed above, also indicated that reduction in CMAP amplitudes in critically ill patients is predictive of developing CIP or CIM. In general, nerve function declines as length of ICU stay increases.

Direct Needle Stimulation. In CIP, the neCMAP is reduced, while the dmCMAP is relatively higher, because the nerve dysfunction is bypassed. Thus, the neCMAP to dmCMAP ratio is less than 0.5.

Needle Electrode Examination. In most cases, needle electrode examination reveals fibrillation potentials and positive waves in distal and proximal muscles in a multifocal pattern with variable severity. Such signs of denervation may be present in facial muscles. Fibrillation potentials are usually noted after 2 weeks, but they have been reported as early as 7–9 days after initiation of mechanical ventilation and 2–5 days after ICU admission, but the time of onset of CIP is often difficult to pinpoint.

MUPs exhibit decreased recruitment. Their morphology varies depending on the timing of the study. Acutely, MUP morphology is normal. Within weeks of onset, low amplitude, polyphasic, “nascent,” reinnervating MUPs have been reported, and long duration MUPs are typical weeks to months after onset in association with reinnervation. With regard to study of the diaphragm, Zifko et al. reported fibrillation potentials in 29% of examined patients along with reduced MUP recruitment in 47%.

PATHOPHYSIOLOGY AND ANIMAL MODELS

CIM. The main histopathologic features of CIM are myofiber atrophy (worse in type 2 fibers), myofibrillar disorganization, and selective myosin (thick filament) loss. Phrenic CMAPs are also often reduced. The thick filament loss may be subtle. It is more likely to be identified 14 days after disease onset and is much more likely by 30 days ± 11 days after IVCS exposure. The degree of necrosis and regeneration is variable, ranging from none to severe. Immunohistochemical, biochemical, and genetic findings include calpain upregulation, increased apoptosis, decreased myosin transcription rate, loss of sarclemmal nitric oxide synthase, and upregulation of the transforming growth-B/mitogen activated protein kinase pathway. The primary disease pathway is undetermined, but alterations in all or some of these pathways may be driven by sepsis or corticosteroids. Inactivity and cachexia of critical illness may also lead to upregulation of cell signaling molecules such as myogenic differentiation factor D that also affect other muscle specific genes, including those that code for myosins. Of interest, a noncritical illness rodent model of myosin loss was developed more than 20 years ago. It uses intaperitoneal corticosteroids followed...
by sciatic nerve transection and results in myosin loss in the calf muscle. More recent studies identified selective depletion of myosin mRNA and muscle membrane inexcitability due to sodium channelopathy. In addition, Friedrich et al. took fractionated sera from patients with CIM, applied it to single intact voltage-clamped muscle fibers, and found impaired calcium channel function and enhanced myofiber shortening that might account for reduced calcium release from the sarcoplasmic reticulum along with decreased force in patients with CIM. On the other hand, in the denervation-steroid animal model, increased calcium ion release from the sarcoplasmic reticulum with increased ryanodine receptor 1 activity was demonstrated.

CIP. From autopsy and biopsy specimens, the typical histopathologic finding is degeneration of motor and sensory axons, although nerve biopsies are sometimes normal. Inflammatory cells are rarely present. The precise cause of axonal degeneration is not known. It is thought that inflammatory cytokines and microvascular dysfunction associated with SIRS lead to axonal degeneration and injury to other tissues. A more specific toxic humoral factor is being sought. Hyperglycemia, hypoalbuminemia, and nutritional factors may increase the risk.

**FIGURE 7.** Critical illness myopathy with loss of myosin thick filaments. (A) Myosin ATPase reacted cryostat section at pH 9.4. The darkly staining myofibers are atrophic type 2 fibers. The type 1 fibers stain lightly. Some fibers with myosin loss are not reactive (arrows). (B) Serial section reacted with myosin ATPase at pH 4.6 reveals that the same myofibers are nonreactive (arrows), and there is patchy reactivity in some darker type 1 fibers. Scale bar = 40 microns. (C) An electron photomicrograph shows normal myofibrils at the top with intact A bands (A) containing thick filaments. The majority of the myofibrils below lack A bands. The thin dark Z-bands are preserved throughout the myofiber.

**FIGURE 8.** Illustration of factors involved in the development of critical illness myopathy and polyneuropathy. A critically ill patient is undergoing mechanical ventilation and treatment for critical illness. The pathways that are associated with development of CIM or CIP are noted, and overlap does occur. Beneath ‘axon injury’ is an illustration of a teased nerve fiber exhibiting axonal degeneration; beneath ‘Membrane inexcitability’ is an illustration of loss of thick filaments. Abbreviations: TGFβ-MAPK, transforming growth factor-β/mitogen activated protein kinase. Dec MHC, decreased myosin heavy chain. See text for additional information on pathophysiology.
There is a septic animal model of CIP produced by cecal ligature and perforation. The model exhibits reductions in rat tail mixed nerve conduction consistent with a neuropathy, and there is also a decreased sodium current with reduced muscle excitability and a denervation-like state. Thus, reduced sodium current could play a role early on in CIP.

In Figure 8, an overview of mechanisms involved in the development of CIM and CIP is shown.

PREVENTION, MANAGEMENT AND OUTCOMES

Intensive insulin treatment of hyperglycemia reduces the frequency of CIM/CIP in ICU patients, but the data are somewhat difficult to decipher, because the populations are generally lumped together. The topic was reviewed by Wieske, who concluded that there are conflicting data about the beneficial effect of strict glucose control and the duration of mechanical ventilation in CIP and CIM. There is also possible increased mortality with intensive treatment of hyperglycemia.

Daily electrical stimulation might be useful in preventing the development of neuromuscular weakness in critically ill patients and in shortening the duration of weaning from mechanical ventilation. This warrants further study.

Because IVCS are a likely risk factor for CIM, only judicious use of IVCS is recommended in ICU patients to possibly reduce CIM occurrence, especially because CIM can reoccur with repeated IVCS exposure. Avoiding or minimizing use of paralytic drugs has also been advised, without proven benefit. Patients treated in the ICU could be monitored for development of CIM/CIP with serial fibular motor NCS. Because CK levels are usually elevated with CIM, it is likely that serial CK measurements could be used for screening.

Once CIM or CIP arise, aggressive treatment of underlying illnesses is advised along with supportive care, routine prophylaxis for deep venous thrombosis, and pulmonary toilet. This topic was reviewed recently by Chawla and Gruener. There are no specific treatments.

The mortality associated with CIP and sepsis is up to 50%. Survivors have variable outcomes. Patients with mild CIM and CIM recover within weeks. Patients with more severe disease usually require inpatient rehabilitation starting with passive range of motion, early mobilization, and then usually intense physiotherapy. Patients must be reassured that they will improve.

Long-term study data show that patients with CIM have better outcomes than those with CIP. Using DMS and electrophysiologic testing, Koch et al. found that patients with both CIM and CIP develop electrophysiologic features of CIM first. Pure CIM patients are less weak and get out of the hospital sooner than those with CIM and CIP. In another interesting study, 42 of 124 consecutive ICU patients admitted to a neurorehabilitation unit had CIM (71%), CIM (14.5%), or both.
(14.5%). 54% had good functional recoveries, and most improved over 6–12 months. A total of 76% went home; some were readmitted to rehabilitation, and a minority were placed in long-term care facilities. The patients with persistent disabilities all had CIP with or without CIM and central nervous system insults. None had CIM alone. One-year outcomes of 13 survivors in the CRIMYNE study were: complete recovery in 3–6 months for CIM; a mixture of tetraplegia, partial recovery, and full recovery in CIM/CIP patients; and full recovery in a minority of CIP patients with more having persistent muscle weakness or tetraparesis.

In patients with both CIM and CIP, sophisticated studies using DMS as well as motor unit number estimates have suggested primarily myopathic injury in the majority. It is very important to try to achieve such diagnostic certainty in research studies to identify risk factors and better define outcomes. The features noted in Table 3 are the primary elements used for diagnosis in addition to excluding other causes of neuromuscular disease. In addition, the identification of myosin loss on muscle biopsy can also be used to confirm a diagnosis of CIM, and an elevated CK is a supportive feature. On the other hand, it has been argued that critical illness neuromuscular weakness should be considered a mixed entity. In clinical practice, it probably is not as important to fully differentiate CIP and CIM unless obtaining additional prognostic information is paramount, because CIM has a better prognosis than CIP.

Phrenic nerve stimulation may also be performed in patients with ventilatory failure when feasible. In addition, NCS may also be used to monitor ICU patients for development of CIM/CIP. Lastly, muscle biopsy can be used to confirm a diagnosis of myopathy, but unless myosin loss is present, the findings may not be very specific for CIM. We usually only obtain muscle biopsy specimens if other causes of myopathy; e.g., myositis, are under consideration or if obtaining prognostic information associated with a diagnosis of CIM is critical.

This study was reviewed and approved by committees of the AANEM. It did not undergo further peer review by Muscle & Nerve.

**REFERENCES**


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