Acquired Neuromuscular Weakness in Critical Illness

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Objectives

Objectives - (1) Discuss the clinical presentation, diagnosis, management, and outcomes of NM weakness associated with critical illness, (2) explain a unifying hypothesis for the pathophysiology for this common complication, (3) describe the frequency and risk factors for NM weakness in the ICU setting, (4) demonstrate clinical and EDX approaches, (5) present a proposed pathophysiology for the condition, and (6) provide examples of rehabilitation considerations.

Target Audience:

• Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
• Health care professionals involved in the diagnosis and management of patients with neuromuscular diseases
• Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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Neuromuscular Effects of Critical Illness: Frequency, Risk Factors, and Outcomes

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INTRODUCTION

The incidence and specific risk factors of critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM) are difficult to define precisely. Studies that have addressed these epidemiologic issues vary in many important ways. The patient populations studied differ in disease severity as well as the way in which the severity is measured (e.g., presence of severe sepsis, multi-organ failure, need for mechanical ventilation, timing of assessment, etc.). These studies also differ in the diagnostic category for inclusion. Some studies address only CIP, some CIM only, but many include patients with features of either disease. Lastly, the diagnostic criteria differ widely. Some studies rely on clinical criteria while others incorporate electrophysiologic studies as well.

FREQUENCY

The incidence of CIP and/or CIM appears to be about 33-50% of patients who are critically ill in the intensive care unit (ICU) and on a mechanical ventilator. This has been demonstrated in small, but well-performed, single-site prospective studies, as well as larger multi-center ones (Table 1). Two excellent studies address this issue from this very different perspective, but they reach the same conclusion. Khan and colleagues conducted a prospective cohort study of patients with severe sepsis in the ICU. Twenty patients survived the analysis period and half (50%) of those developed CIP, CIM, or features of both, most by day 14 of illness. They also found that, of those affected, 10% had CIP, 10% had CIM, but 80% had evidence of both disorders. Stevens and colleagues performed a systematic review of 24 studies (19 prospective) of critically-ill patients who developed CIP and/or CIM. Most of these studies avoided the problem of distinguishing between CIP and CIM by combining them in some fashion as an endpoint (see below). Of the total 1,421 patients in these studies, 46% (655 patients) developed one or both of these disorders.

The 46% incidence of CIP and/or CIM in the large, systematic review by Stevens and colleagues is remarkably similar to the 50% incidence found by Khan and colleagues. In this systematic review, studies with more than 10 patients were included in the analysis if they met two criteria. The first was that the study enrolled patients in the ICU and they had electrodiagnostic (EDX) findings or a combination of clinical and EDX findings, with the EDX tests obtained in at least all of the patients who had positive clinical findings. The second was that they compared the patients with CIP and/or CIM with patients in the ICU who had negative clinical and/or EDX findings.

Khan and colleagues conducted a prospective cohort study of patients with severe sepsis in the ICU. Commonly-used modified systemic inflammatory response syndrome (SIRS) criteria were used as the definition of severe sepsis. Patients had neurologic examinations and nerve conduction studies (NCSs) performed within 72 hours of developing severe sepsis which were then repeated weekly until ICU discharge or death. NCSs and needle electromyography (EMG) were performed on those who developed clinical weakness.

Many of the studies that have reported the incidence of these disorders have combined CIP and CIM as one, requiring only features of one or both for inclusion. This seems wise since there is evidence that they frequently coexist, as noted in 80% of the affected individuals reported by Khan and colleagues. Also, it may be difficult to differentiate one from the other definitively.
There is a large cohort of patients in the ICU who have clinical and EDX features common to both disorders. These patients are not as easily classified as purely CIP or CIM. The clinical presentation of both disorders is dominated by limb weakness that develops in the ICU, usually accompanied by a delay in weaning the patient from mechanical ventilation. On electrophysiologic examination, one typically finds features common to both disorders. This includes reduced compound muscle action potential (CMAP) amplitudes on NCSs. Sensory NCSs are often hampered by technical factors (limb edema and electrical noise from the ICU equipment), or the sensory responses may be low amplitude due to pre-existing neuropathy. Furthermore, the assessment of motor unit action potential morphology and recruitment is often limited by the patient’s encephalopathy or sedation. Direct muscle stimulation and measures of the CMAP duration may be helpful in identifying CIM, but specific diagnostic criteria for these techniques have not been formally established. Of course, establishing the presence of CIM by direct muscle stimulation or prolonged CMAP amplitudes does not address the presence or absence of CIP.

In addition to the study of Khan and coworkers, there are several other large prospective studies that use reasonably rigorous neurologic and EDX assessments to report the incidence of CIP and/or CIM. Most do not attempt to reliably distinguish the two disorders. The incidence of ICU-acquired weakness was reported to range 25-57% in these studies. De Letter and colleagues reported 98 patients who had been in the ICU and on a mechanical ventilator for at least 4 days. Starting on day 4, the patients had biweekly neurologic examinations and NCSs/needle EMG on days 4, 11, and 25. For inclusion, the patients needed both clinical and EDX evidence of CIP and/or CIM. They found ICU-acquired weakness in 33%. De Jonghe and coworkers evaluated 95 patients on mechanical ventilation for more than 7 days. They screened patients on day 7 and those who were significantly weak were identified as having CIP and/or CIM. They found that 25% of the patients met this criterion. All had NCS evidence of CIP and half also had biopsy evidence of myopathy. Bednarik and colleagues studied 60 patients in the ICU who had a sequential organ failure assessment (SOFA) grade of 3 or 4, but mechanical ventilation was not a requirement. The patients had a neurologic evaluation daily for 28 days and EDX studies in week 1 and again in week 5. These authors found clinical evidence of CIP and/or CIM in 28% and electrophysiologic evidence in 57%. They believed that of those affected 40% had CIM, 34% had CIP, and 26% had features of both.

Latronico and coworkers reported 90 patients in the ICU who had a simplified acute physiology score (SAPS II) greater than 35. Patients were assessed only by EDX studies starting 24 hours after ICU admission. Patients had daily simple NCSs and weekly complete studies (NCSs and needle EMG) until ICU discharge. They found evidence of CIP and/or CIM in 30% of patients.

A few studies have limited their inclusion criteria to the presence of CIP alone. Given that CIP and CIM frequently coexist, these studies may underestimate the presence of ICU-acquired weakness.

### Table 1. Major prospective studies: reporting the combined incidence of critical illness polyneuropathy and/or critical illness myopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Definition of CIP/CIM</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevens and colleagues21</td>
<td>Systematic review of 24 studies (19 prospective)</td>
<td>Clinical and electrodiagnostic, or electrodiagnostic, evidence of either</td>
<td>46%</td>
</tr>
<tr>
<td>Khan and colleagues14</td>
<td>Cohort study of 20 surviving patients with severe sepsis</td>
<td>Clinical and electrodiagnostic evidence of either</td>
<td>50%</td>
</tr>
<tr>
<td>De Letter and colleagues9</td>
<td>98 ICU patients on a mechanical ventilator for &gt;4 days</td>
<td>Clinical and electrodiagnostic evidence of either</td>
<td>33%</td>
</tr>
<tr>
<td>De Jonghe and colleagues7</td>
<td>95 ICU patients on mechanical ventilation &gt;7 days</td>
<td>Clinical evidence of either</td>
<td>25%</td>
</tr>
<tr>
<td>Bednarik and colleagues2</td>
<td>60 ICU patients; SOFA score 3 or 4; did not require mechanical ventilation</td>
<td>Clinical or electrodiagnostic evidence of either</td>
<td>Clinical and electrodiagnostic evidence in 28%</td>
</tr>
</tbody>
</table>

CIM=critical illness myopathy, CIP=critical illness polyneuropathy, EMG=electromyography, ICU=intensive care unit, NCS=nerve conduction study, SOFA=sequential organ failure assessment
neuromuscular disease. On the other hand, several of these studies use EDX criteria alone for inclusion, which undoubtedly overestimates the incidence of clinically-relevant disease. One early, illustrative prospective study detailed 43 ICU patients who had sepsis and multiple organ failure. The patients were in the ICU for a mean of 28 days when evaluated and all had septic encephalopathy. Thirty-five percent had clinical findings consistent with neuropathy, defined by the study authors as distal weakness and hyporeflexia or inability to wean from the respirator. More than half (70%) had electrophysiologic evidence of an axonal neuropathy. Other large prospective studies have reported the incidence of CIP from 47 to 63%. Leijten and coworkers reported 38 patients in the ICU on mechanical ventilation for more than 7 days. They found evidence of CIP by NCS and needle EMG criteria alone in 47%. Zifko and colleagues studied 132 patients who had SIRS, were on mechanical ventilation, and were referred for EDX studies. They found clinical and EDX evidence of CIP in 47%. Since patients were referred for EDX studies, this report likely overestimates the frequency of CIP. Garnacho-Montero and colleagues reported 73 patients who were septic with multiple organ failure and on mechanical ventilation. These authors also used only NCS and needle EMG criteria for inclusion and found CIP in 63%.

There are few studies that have reported the incidence of CIM alone. Amaya-Villar and coworkers reported a cohort of patients with an exacerbation of chronic obstructive pulmonary disease who were on mechanical ventilation and treated with high-dose intravenous corticosteroids. These authors identified CIM by needle EMG criteria alone. NCSs were not performed. They found evidence of CIM in 35%. Myopathy was confirmed by muscle biopsy in a subset of these patients. Campobello and colleagues reported 100 consecutive patients in the ICU after liver transplantation who also received intravenous corticosteroids as well as neuromuscular blocking agents. They found evidence of CIM on EDX studies (and muscle biopsy in most affected) in 7%. However, they limited their inclusion to only those patients who had less than antigravity strength. This likely significantly underestimated the true incidence of CIM in this cohort.

**RISK FACTORS**

Three large (61-95 patients each) prospective studies have examined risk factors in critically-ill patients for the development of neuromuscular weakness. All agree that measures of illness severity [e.g., acute physiology, age, chronic health evaluation (APACHE) III score, presence of SIRS, or organ failure assessment scores] correlate with the development of CIP and/or CIM. The likelihood of developing CIP and/or CIM is strongly influenced by increasing severity of illness. De Letter and coworkers showed that for those with a high APACHE III score (>85) and the presence of sepsis at the time of study entry (day 4 of mechanical ventilation), the probability of developing CIP and/or CIM by 30 days was 72%. This compares to only 8% in patients with low APACHE III scores (<70) and no sepsis. This is almost a 10-fold higher risk in severely-ill, septic patients. In the limited data available as multivariable analyses, CIP and/or CIM was independently associated with the APACHE III score 30 days after mechanical ventilation with an odds ratio (OR) of 5.2 (95% CI: 2.8-9.8) and the SOFA score 1 week after ICU admission with a relative risk (RR) of 2.4 (1.0-5.5). The presence of sepsis or SIRS is also a significant risk factor for the development of CIP and/or CIM. The univariable relation of sepsis with the development of disease has been reported in 12 separate reports. The association ranged from an OR of 2.4 (0.8-6.8) to 49 (4.7-519). In the two reports that performed a multivariable analysis, the independent association between SIRS and CIP/CIM was clear. The RR in those with SIRS 1 week after admission was 3.74 (1.4-10.2) and the OR in those who had SIRS 30 days after the start of mechanical ventilation was 2.5 (1.2-4.80).

The caussative association between high-dose corticosteroids and nondepolarizing neuromuscular blocking agents (NMBAs) with ICU-acquired weakness, particularly for CIM, is likely. The first reports of CIM were in patients with status asthmaticus treated with high-dose corticosteroids and NMBAs. Many of the early reports of critically-ill patients with severe CIM emphasized the prodromal use of corticosteroids and NMBAs. However, the results from prospective trials have been inconsistent. Of the reports that detailed this information, there was no significant univariate association with corticosteroids or NMBAs. Multivariable analysis identified a relationship between corticosteroids and CIP/CIM in one of the two studies that addressed this. In this study, the use of corticosteroids was a significant risk factor (OR 14.9). Similarly, one of three studies that did multivariable analysis showed an association of CIP/CIM with NMBAs (OR 16.32). One major limitation of the prospective studies that did not show an association was the relatively small number of patients included who had received substantial doses of corticosteroids and/or NMBAs.

Hyperglycemia is certainly associated with the presence of CIP and/or CIM, but whether it is an independent risk factor for these disorders has not been established. The blood glucose is higher in those who develop ICU-acquired weakness than in those who do not in virtually all studies that have reported this data. For example, De Jonghe and colleagues, in their prospective study of 95 critically-ill patients, noted that the mean serum glucose was significantly increased at 360 mg/dL in those who developed CIP/CIM versus 239 mg/dL in those who did not. Two randomized controlled trials by the same authors showed a lesser incidence of CIP and/or CIM in those treated with insulin therapy (blood glucose target 80-110 mg/dL) than in those who were treated in a conventional fashion (blood glucose target 180-200 mg/dL). In the first study, the authors performed weekly needle EMG studies on 405 patients who were in the surgical ICU for more than 7 days and randomized two treatments to these patients. They were classified as having CIP and/or CIM by the presence or absence of fibrillation potentials and positive sharp waves. NCSs and needle EMG with voluntary contraction were not performed. They found an incidence of CIP/CIM of 49% in the conventionally treatment arm, but only 25% in the insulin therapy cohort. In the second study, similar methods were used and it looked at the incidence of CIP/CIM in 443 patients in the medical ICU for longer than 7 days. The incidence of CIP/CIM was 51% in the conventionally treated group and 39% in the insulin therapy group. However, the conclusions of both studies are limited by the inadequate definition of CIP/CIM (identified by the presence of fibrillation potentials alone without NCS or clinical signs).
There are a number of other less clinically-significant risk factors that may be associated with the development of CIP and/or CIM (Table 2). The individual studies that propose these other risk factors are detailed in a recent review by Latronico and Bolton. These other likely risk factors include renal failure and renal replacement therapy, parental nutrition, low serum albumin, and hyperosmolality. The use of aminoglycoside antibiotics are found to be a risk factor in some studies, but not in a number of other studies.18,21

OUTCOMES

There is substantial evidence that the development of CIP and/or CIM in a critically-ill patient will prolong the ICU stay and hospital course. Large, prospective trials have demonstrated that the presence of these disorders more than doubles the time it takes to wean the patient from mechanical ventilation. For example, in a prospective study of 64 ICU patients on a ventilator for more than 6 days, those who developed CIP and/or CIM had a mean ventilator time of 34 days compared to 14 days for those who did not develop weakness.10 The presence of CIP and/or CIM also substantially increases the time of the ICU and hospital stay. In the study by Garnacho-Montero and colleagues the mean ICU stay of those with ICU-acquired weakness was 47 days versus 23 days in patients who did not develop CIP and/or CIM. Even in patients solely with CIM, the mean hospital stay was 49 days versus 14 days in those who did not develop CIM.4

Koch and coworkers report data that, not surprisingly, shows that the development of both CIP and CIM leads to a longer ICU stay than those with CIM alone. They prospectively examined 53 patients who were critically-ill (SAPS II >20) and on a mechanical ventilator. The mean ICU stay in those who did not develop CIP and/or CIM was 8 days. This contrasted with 10 days in those with CIM and 32 days in those with both CIP and CIM. They did not find sufficient numbers of patients with clinical and electrophysiologic criteria of CIP alone to include that group in the analysis.

There is a high mortality rate in patients with CIP and/or CIM due to the underlying critical illness. Although not a consistent finding in prospective studies in the ICU,22 many studies have found that mortality is higher in patients who develop weakness due to critical illness.1,4,10,14,15 However, this is difficult to separate from the underlying severity of illness. The one study that did explore ICU mortality in a multivariable model did find that CIP and/or CIM is an independent predictor of reduced survival.10

Patients with purely CIM who survive the period of critical illness usually recover within 1-3 months.6,16 David and colleagues found that all patients with CIM had recovery to near functional independence within 1 month of extubation. They found that the rate of recovery did not appear to be correlated with the severity of the electrophysiologic findings (degree of mean CMAP amplitude reduction), the degree of serum creatine kinase elevation, or the presence or absence of spontaneous activity (fibrillation potentials or positive sharp waves) on the needle EMG examination.
REFERENCES

The Approach to Neuromuscular Weakness in Critical Illness

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INTRODUCTION

Weakness in patients with critical illness is not only encountered in the intensive care unit (ICU), but in general hospital wards, outpatient clinics, EMG laboratories, and rehabilitation facilities. Electrodiagnostic (EDX) testing is essential in all these situations. The following case report illustrates the problem in the outpatient clinic.

Case Report

A 55-year-old air traffic controller was seen in the neurology clinic for a 2-year history of lower extremity weakness. The cause of his neuromuscular weakness was undiagnosed and he had not been seen by a neurologist or physiatrist nor had any EDX studies. He reported difficulty climbing stairs and rising from toilet. He also complained of numbness and tingling in his hands and feet. In addition to his motor and sensory complaints, he reported slow thought process, spacial disorientation, impaired recent memory, headaches, and an unsteady gait.

His past medical history was remarkable for an admission to the critical care unit after loss of consciousness that was due to a septic shock related to a dental abscess. While in the critical care unit, he was put on a ventilator for respiratory support. After discharge he experienced slow recovery from his neurological symptoms.

On examination, he was found to have a grossly normal mental status. He had reduced deep tendon reflexes and vibratory sensory deficits in his feet. His gait was mildly unsteady. Initial serum workup was negative for liver and renal dysfunction and endocrine abnormalities. He had normal serum levels of creatinine kinase, lactate and electrolytes. His folate and vitamins B12 and B6 levels were within the normal range. Serum protein electrophoresis and antinuclear factor was unremarkable.

Nerve conduction studies (NCSs) of the sensory nerves showed diminished response in the upper extremity and absent response in the lower extremity. There was also diminished response in the tibial motor nerve. Needle electromyography (EMG) showed large polyphasic units. This patient’s history and clinical presentation is typical of acquired neuromuscular injury during critical illness.

NEUROMUSCULAR DISEASE IN THE INTENSIVE CARE UNIT

There have been significant advances in the diagnosis, management, and prognosis of neuromuscular diseases in the intensive care setting. It is now recognized that critical illness polyneuropathy (CIP) is the most common polyneuropathy in an intensive care setting. Well over a third of the patients who are severely ill in the critical care unit have been shown to have CIP. Sometimes, a primary myopathy in exclusion of polyneuropathy is observed and this condition is now referred to as critical illness myopathy (CIM). Ultimately, the motor deficits can be attributed to CIP, CIM, or a combination of both. There is often limb weakness associated with the respiratory muscle weakness. While the mental status is grossly normal, stupor or coma due to sedatives or septic encephalopathy can be present.

Critical care intensivists will ask for neurological consultation and electrophysiological studies in patients who have unexplained difficulty in weaning from the ventilator and, often, limb...
The approach to neuromuscular weakness in critical illness

Weakness. It is important to consider generalized neuromuscular disorders that can be associated with critical illness (Table 1). One must also exclude neuromuscular conditions that had developed before admission to the ICU (Table 2). Sudden respiratory insufficiency, often precipitated by infection, would prompt intubation and placement on a ventilator. Performing EDX studies in the ICU might be challenging; nevertheless, comprehensive electrophysiological studies can be extremely helpful and can suggest the underlying diagnosis; e.g., motor neuron disease, myasthenia gravis, muscular dystrophy. CIP, CIM, or a combination of both may be suspected in the ICU when, on testing for the level of consciousness by compressing the nail bed, one observes absent limb movement, but facial grimacing. Tendon reflexes are not always absent, and sensory testing is difficult. These clinical signs may be similar in both CIP and CIM. Profound muscle weakness and wasting may occur solely from disuse atrophy as a result of prolonged recumbency in the ICU bed. In this situation NCSs and needle EMG are normal and muscle biopsy is normal or shares type II atrophy. Early physiotherapy may improve muscle strength.

### Differential Diagnosis

The features differentiating CIP/CIM from other neuromuscular disorders in critical illness are shown in Table 1. Transient neuromuscular blockade is not uncommon in patients receiving high doses of neuromuscular blocking agents. Although there are clinical similarities between transient neuromuscular blockade and CIP/CIM, repetitive nerve stimulation (RNS) studies can help distinguish between them. Patients admitted to the ICU with a diagnosis of Guillain–Barré syndrome (GBS) may have worsening symptoms related to mechanical ventilation, development of sepsis or multiorgan dysfunction. Worsening of the peripheral neuropathy in these patients might be attributed to exacerbation of the GBS, which in turn might prompt further attempts of immunosuppression. If the electrophysiologic studies in these patients reveal axonal degeneration, CIP should be considered as the more likely cause and instead of immunosuppression the management of systemic inflammatory response syndrome (SIRS) should be the primary focus. That being said, there is some evidence to suggest that axonal loss can develop in GBS patients

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Type</th>
<th>Incidence</th>
<th>Clinical features</th>
<th>Electrophysiological findings</th>
<th>Serum creatine kinase</th>
<th>Muscle biopsy</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Critical illness polyneuropathy</td>
<td>Common</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Axonal degeneration of motor and sensory fibers</td>
<td>Nearly normal</td>
<td>Denervation atrophy</td>
<td>Variable</td>
</tr>
<tr>
<td>Neuromuscular transmission defect</td>
<td>Transient neuromuscular blockade</td>
<td>Common with neuromuscular blocking agents</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Abnormal repetitive nerve stimulation studies</td>
<td>Normal</td>
<td>Normal</td>
<td>Good</td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td>Thick-filament myopathy</td>
<td>Common with steroids, neuromuscular blocking agents, and sepsis</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Abnormal spontaneous activity</td>
<td>Mildly elevated</td>
<td>Loss of thick (myosin) filaments</td>
<td>Good</td>
</tr>
<tr>
<td>Acute myopathy and scattered necrosis</td>
<td>Common</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Myopathy</td>
<td>Mildly or moderately raised</td>
<td>Scattered necrosis</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Acute myopathy with diffuse necrosis (necrotising myopathy of intensive care)</td>
<td>Rare</td>
<td>Flaccid weakness, myoglobinuria</td>
<td>Severe myopathy</td>
<td>Greatly raised, myoglobinuria</td>
<td>Marked necrosis</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Disuse (cachectic) myopathy</td>
<td>Common</td>
<td>Muscle wasting</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or type II fiber atrophy</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Rare</td>
<td>Flaccid limbs</td>
<td>Near Normal</td>
<td>Markedly elevated myoglobinuria</td>
<td>Normal or mild necrosis</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Combined polyneuropathy and myopathy</td>
<td>Common</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Indicative of combined polyneuropathy and myopathy</td>
<td>Variable</td>
<td>Denervation atrophy and myopathy</td>
<td>Variable</td>
<td></td>
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</tbody>
</table>
Table 2. Differential diagnosis in the intensive care unit of the syndrome of rapidly developing limb and respiratory muscle weakness

<table>
<thead>
<tr>
<th>Weakness before admission</th>
<th>Weakness after admission</th>
</tr>
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<tbody>
<tr>
<td>Disorders of spinal cord</td>
<td></td>
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<tr>
<td>Traumatic myelopathy</td>
<td>Acute transverse myelitis</td>
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<tr>
<td>Acute epidural compression from neoplasm, infection</td>
<td>Acute ischemia</td>
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<tr>
<td>Motor neuron disease</td>
<td></td>
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<tr>
<td>Acute Polynuropathies</td>
<td></td>
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<tr>
<td>Guillain–Barré syndrome</td>
<td>Critical illness polyneuropathy</td>
</tr>
<tr>
<td>Axonal forms of Guillain–Barré syndrome</td>
<td>Motor neuropathy (neuromuscular blockers)</td>
</tr>
<tr>
<td>Miller-Fisher syndrome</td>
<td></td>
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<tr>
<td>Chronic polynuropathies</td>
<td></td>
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<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
<td>Chronic polynuropathies plus sepsis</td>
</tr>
<tr>
<td>Diabetic polyneuropathy</td>
<td></td>
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<tr>
<td>Neuromuscular transmission defects</td>
<td></td>
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<tr>
<td>Myasthenia gravis</td>
<td>Neuromuscular blockers</td>
</tr>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td></td>
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<tr>
<td>Hypocalcemia</td>
<td></td>
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<tr>
<td>Hypermagnesemia</td>
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<tr>
<td>Organophosphate poisoning</td>
<td></td>
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<tr>
<td>Wound botulism</td>
<td></td>
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<tr>
<td>Tick-bite paralysis</td>
<td></td>
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<tr>
<td>Myopathy</td>
<td></td>
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<tr>
<td>Muscular dystrophy: e.g., Duchenne’s, myotonic</td>
<td>Cachectic myopathy</td>
</tr>
<tr>
<td>Acute necrotizing myopathy: myoglobinuria</td>
<td>Necrotizing myopathy of intensive care</td>
</tr>
</tbody>
</table>

in the absence of the usual precipitants of CIP. The axonal variants of GBS (acute motor and sensory axonal neuropathy, and acute motor axonal neuropathy) can be distinguished from CIP by the presentation of the symptoms or signs prior to ICU admission (Table 2). Finally, mononeuropathies and plexopathies can affect patients in the ICU. These can occur in isolation, or coexist with CIP/CIM. Prolonged immobility, direct trauma, ischemia, and hemorrhagic compression can precipitate such a presentation.

ELECTROPHYSIOLOGICAL FEATURES

It is useful to consider the following electrophysiological approach in a patient suspected to have a neuromuscular disease in the ICU. The skin temperature should be recorded before the study, as ICU patients are often cool. Needle EMG of the limbs will show varying degrees of positive sharp waves and fibrillation potentials both in CIP and CIM. Motor unit action potentials (MUAPs) can be normal or mildly myopathic in both CIP and CIM; thus they will not help distinguishing the two. If consciousness is depressed and muscles are not activated, MUAPs might not be recordable. Needle EMG of the intercostals and the diaphragm provide valuable information regarding the type and extent of respiratory muscle involvement. An ultrasound-guided needle EMG can help. Needle EMG of the diaphragm in a patient with CIP should reveal few MUAPs with attempted inspiration and only denervation potentials might be recorded. Polyphasic units may become apparent later on as a sign of reinnervation. Later, the amplitude of these MUAPs increases in CIP.

After completion of the needle EMG studies, narcotic analgesia can be utilized for the remainder of the NCSs, which may include phrenic, motor, and sensory studies of the limbs. Studies in the limbs of a patient with CIP show amplitude attenuation both in the compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). Nerve conduction velocities in CIP are either normal or mildly affected. NCSs can help distinguish CIP from CIM. Similar to CIP, there is a drop in amplitude in CMAPs in CIM; however, SNAPs are normal in CIM. The duration of CMAPs in CIP is not prolonged, whereas prolonged duration of CMAPs is an important feature of CIM. In fact, the increase in CMAP duration has been shown to correlate well to the severity of the disease in CIM. Prolongation of CMAP duration is more evident in the lower extremities and it can be three times as long when compared to healthy control subjects. There is also direct evidence of reduced muscle excitability through direct stimulation of the muscle in CIM in contrast to CIP. Direct muscle stimulation can therefore be used to distinguish CIM from CIP. In CIM, the ratio of the nerve stimulated CMAP in relation to the direct muscle stimulated CMAP is less than 0.5 and the amplitude of the CMAP after direct muscle stimulation is less than 3 mV.

Phrenic NCSs can be safely performed in the ICU. In a patient with CIP, the CMAP is reduced or absent in the diaphragm with stimulation of the phrenic nerve. One might observe an initial positive deflection with a short latency from activation of the chest wall muscles by the inadvertent stimulation of the brachial plexus. Needle EMG of the diaphragm will reveal fibrillation potentials and positive sharp waves. If the phrenic NCS is nondiagnostic and a defect in the neuromuscular junction is suspected, performing RNS at 3 Hz and 30-40 Hz is needed. The RNS study should be performed while the patient is under narcotic sedation. Otherwise, the selection of the nerve to be studied should be guided by the clinical findings. The reader’s attention is drawn to the excellent recent review by David Lacomis on electrophysiological studies in critical illness.

DIAGNOSTIC CRITERIA

Definitive diagnosis of CIP can be established when: (1) the patient is critically ill with a single- or multiorgan failure, (2) there is limb weakness or difficulty weaning the patient of the ventilator in the absence of cardiopulmonary cause, (3) there is EDX evidence of mixed sensory and motor axonal polyneuropathy, and (4) a dysfunction of neuromuscular junction is excluded with an RNS study. A probable diagnosis of CIP can be made even in the absence of a clinically demonstrated weakness or difficulty with ventilatory weaning, as long as the other diagnostic criteria are met (Table 3).
THE APPROACH TO NEUROMUSCULAR WEAKNESS IN CRITICAL ILLNESS

Table 3. Diagnostic criteria for critical illness polyneuropathy

1. The patient is critically ill (multiorgan failure).
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded.

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.

Table 4. Diagnostic criteria for critical illness myopathy

1. The patient is critically ill (multiorgan failure).
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 action 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 noncollaborative patients.
6. Absence of a decremental response on repetitive nerve stimulation.
7. Muscle histopathological findings of primary myopathy (e.g., 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

PATHOPHYSIOLOGY

The pathophysiologic process leading to multiorgan dysfunction and failure in the critically ill patient is likely integral to the process leading to CIP and CIM. Thus, microcirculatory, cellular, and metabolic mechanisms are involved to some extent in the process leading to CIP and CIM.

Microcirculatory dysfunction has been proposed as a key mechanism in causing distal axonopathy in CIP. The profound disturbance in microcirculation impairs the delivery of essential nutrients to the nervous system. Peripheral nerves have been shown to undergo Wallerian-like degeneration under ischemic conditions lasting more than 3 hours.

Patients with SIRS in the ICU are known to mount a cellular and humoral response. The cellular response involves epithelial and endothelial cells, macrophages, and neutrophils. The humoral response induces the release of various pro-inflammatory mediators. The cellular and humoral response to SIRS in a septic patient leads to impaired perfusion due to excessive vasodilatation through overproduction of nitric oxide, and aggregation of cellular elements through activation of adhesion molecules and deactivation of protein C. The fibrin platelet aggregation and “rolling neutrophils” causes initiation of a cascade of events leading to endothelial damage, increase capillary permeability, and tissue edema.

PROGNOSIS IN CRITICAL ILLNESS

POLYNEUROPATHY AND CRITICAL ILLNESS MYOPATHY

Mortality in CIP has been reported in different series in a range of 21-47%. Although the vast majority of CIP survivors show signs of recovery, they continue to have impaired quality of life with signs of polyneuropathy at 1-2 years. About a third of patients with CIP, CIM, or a combination lose their ability to ambulate independently. Patients with CIP recover slower in general or might not recover. Most notably, in one study all patients had abnormal phrenic nerve conduction during followup studies. Patients with CIM exhibit faster recovery and are more likely to have complete recovery.

Interruption of sedation, or the “least sedation” method, in the critical care patient has been shown to result in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days. During the interruption of sedation, patients with acquired neuromuscular weakness can be reliably identified at an earlier stage, which in turn can help determine which ICU patients are at risk for prolonged ventilatory weaning. Patients identified with weakness would benefit from further workup in terms of imaging of the central nervous system, electrophysiological studies, and possibly muscle biopsy to further help with prognosis. Earlier identification of weakness can also tailor the management and guide the use of neuromuscular blocking agents, sedatives, and steroids since these therapies are thought to predispose to CIM. Rehabilitation decisions can also be made at an earlier stage.
ACQUIRED NEUROMUSCULAR WEAKNESS IN CRITICAL ILLNESS

There is compelling evidence that early physical and occupational therapy can improve outcomes and increase the likelihood of return to independent functional status at hospital discharge. In fact, daily passive mobilization alone can help decrease muscle atrophy in patients with critical illness.

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A Unifying Mechanism for Critical Illness-Associated Neuromuscular Dysfunction

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INTRODUCTION

Intensive care unit (ICU)-acquired weakness is a frequent, serious, and costly health threat. In the United States, more than 750,000 people per year have sepsis with 380,000 requiring intensive care unit (ICU) visits and mechanical ventilation. Studies suggest that from one-third to one-half of patients who require prolonged mechanical ventilation develop global, persistent weakness. From these data, it can be estimated that in the United States from 100,000 to 150,000 patients per year develop profound muscle weakness as a result of critical illness induced by sepsis. This is almost certainly an underestimate of the incidence of ICU-acquired weakness as most patients are not evaluated for mild-to-moderate weakness following critical illness. Development of weakness can greatly prolong the length of hospital stay as patients often require prolonged ventilator support secondary to pulmonary muscle weakness, and they do not regain full strength for many months after their acute illness. Development of weakness has been estimated to raise the average hospital cost per patient by four-fold. Determining the mechanisms underlying weakness in these patients is essential to developing therapy to improve outcome.

CURRENT UNDERSTANDING OF THE MECHANISMS UNDERLYING WEAKNESS FOLLOWING CRITICAL ILLNESS

The first mechanism identified that causes weakness in patients following critical illness was a myopathy, now known as critical illness myopathy (CIM). CIM was identified in patients who had received neuromuscular blocking agents and corticosteroids in the setting of acute pulmonary failure. The mechanisms underlying weakness in CIM were found to be selective loss of fast myosin and severe atrophy of muscle fibers.

Several years after the identification of CIM, a neuropathy was identified in patients recovering from severe sepsis. The neuropathy has come to be known as critical illness polyneuropathy (CIP) and is due to length-dependent degeneration of axons such that distal muscles are more affected than proximal muscles. The cause of the neuropathy is not known, but it occurs most often in patients with sepsis and multisystem organ failure.

It was initially thought that CIP occurred only in patients with sepsis and multisystem organ failure, and CIM occurred only following treatment with neuromuscular blocking agents and corticosteroids. Over time it has become clear that this is not the case. Some patients develop CIM following sepsis in the absence of treatment with neuromuscular blocking agents or corticosteroids. The mechanisms underlying myopathy in sepsis appear to be similar to those occurring in CIM (for review see). A major mechanism underlying reduced force generation by muscle following sepsis is atrophy. Another mechanism is loss of myosin. Many patients appear to have both neuropathy and myopathy. These findings suggest that both CIP and CIM can be caused by sepsis. The co-occurrence of CIP and CIM has led to the terms, “polyneuromyopathy” or critical illness myopathy and/or neuropathy (CRIMYNE). A term which has recently been adopted for the syndrome is intensive care unit-acquired weakness (ICUAW).
SODIUM CHANNELOPATHY IN MUSCLE TRIGGED BY CRITICAL ILLNESS

In the past 15 years, it has become clear that in addition to neuropathy and myopathy there is a third mechanism contributing to weakness: loss of electrical excitability.52 The first indication that there might be an ion channelopathy in critically ill patients came from studies showing that muscle was electrically inexcitable in the acute phase of severe weakness.13,42-44 Subsequently there have been a number of studies demonstrating reduced muscle excitability that manifests as reduction of muscle fiber conduction velocity, increased relative refractory period, and inexcitability of fibers in response to direct muscle stimulation.5,27,33-36 Reduction in muscle fiber conduction velocity likely underlies prolongation of compound muscle action potential duration that is seen in patients with CIM.14

The mechanism underlying reduction of excitability appears to be increased association of sodium channels with inactivation. In mice lacking neuronal nitric oxide synthase (nNOS), denervation-induced loss of excitability was lessened.72 The finding that nNOS is involved in regulation of excitability following denervation adds to earlier findings that implicate nitric oxide in the response of skeletal muscle to denervation.73 Previously, it has been shown that inhibition of nNOS lessens muscle atrophy triggered by denervation.51 As dramatic muscle atrophy occurs in CIM, this raises the possibility that nNOS signaling plays a role in triggering both electrical inexcitability and atrophy of fibers. Further work will be necessary to confirm these preliminary findings.

ARE ELECTRICALLY ACTIVE TISSUES OTHER THAN SKELETAL MUSCLE AFFECTED BY CHANNELOPATHY?

One of the major problems triggered by critical illness is multisystem organ failure. The mechanisms underlying organ failure remain poorly understood. The finding that sodium channelopathy contributes to failure of force generation by skeletal muscle demonstrates a novel form of channelopathy is present during the acute phase of recovery from critical illness. If channelopathy affects other electrically-active tissues, it could provide a mechanism to account for failure of a number of different organ systems.

It is well established that critical illness induces neuropathy. The first indication that neuropathy in critically ill patients might not be entirely accounted for by axon degeneration came from a study in which nerve and muscle biopsies were taken in patients with severe CIP and CIM. Nerve biopsy in many patients with electrophysiologic evidence of neuropathy was normal.26 This suggests there is a functional deficit in nerves of affected patients that does not have a pathological correlate. More recently it was found that nerve excitability is reduced in patients with CIP.57 The presence of a functional deficit in the acute phase of CIP raises the possibility of rapid recovery since restoration of excitability could occur more rapidly than regrowth of axons. Rapid improvement has been reported in some patients with CIP.54 The rate of recovery was more rapid than could be explained by regrowth of axons and thus provides evidence for a functional deficit.

In studies of septic rats, impalement of axons from peripheral nerves reveals reduced excitability.19 The reduction in excitability could not be accounted for by changes in input resistance or resting potential. Instead, restoration of normal excitability following brief hyperpolarization of axons suggests that a hyperpolarized shift in the voltage dependence of sodium channel inactivation is the mechanism underlying reduced excitability.16 These data suggest that a sodium channelopathy similar to the one in skeletal muscle also occurs in peripheral nerve.

When patients with co-occurrence of neuropathy and myopathy are studied longitudinally many evolve into either CIP or CIM.5,15,21 This raises the possibility that sodium channelopathy is present at early stages, but it either recovers more rapidly or evolves into CIP or CIM. If reduced excitability of peripheral nerve and muscle is due to sodium channelopathy, the channelopathy would have to affect multiple sodium channel isoforms. In the rat model of CIM, the sodium channel isoforms present in skeletal muscle are Nav1.4 and Nav1.5.40 In dorsal root axons Nav 1.6 as well as other sodium channel isoforms are expressed.15

Studies of mechanisms underlying loss of muscle excitability in CIM have been performed in a rat model of the disorder. It was found that a combination of a depolarization of the resting potential and a hyperpolarized shift in the voltage dependence of sodium channel inactivation results in inexcitability of the majority of muscle fibers.13,42-44 The voltage dependence of sodium channel inactivation was also found to be shifted in the hyperpolarized direction by sepsis in the rat.46 These data suggest that increased inactivation of sodium channels is a major contributor to reduced excitability.

In normal skeletal muscle only the Nav1.4 sodium channel isoform is expressed. In the rat model of CIM there is upregulation of a second sodium channel isoform (Nav1.5).46 The upregulation of Nav1.5 might cause a hyperpolarized shift in inactivation of the total sodium current. However, through use of toxins the authors were able to determine that the voltage dependence of both Nav1.4 and Nav1.5 are shifted in the hyperpolarized direction in the rat model of CIM. These data suggest that the primary cause of the hyperpolarized shift in inactivation of sodium channels in fibers from the rat model of CIM is a hyperpolarized shift in the voltage dependence of the inactivation of Nav1.4. This represents a novel form of ion channelopathy whereby a change in the behavior of a genetically-normal ion channel is the cause of the disorder. In all previously described channelopathies the mechanism underlying the disorder is a mutation in the channel of interest. If the normal behavior of Nav1.4 could be restored it should be possible to reverse the disorder of excitability.

One finding that may account for the hyperpolarized shift in inactivation is increased association of sodium channels with proteins of the dystrophin-associated protein complex.22 In particular, there is increased association with neuronal nitric oxide synthase. In mice lacking neuronal nitric oxide synthase (nNOS), denervation-induced loss of excitability was lessened.72 The finding that nNOS is involved in regulation of excitability following denervation adds to earlier findings that implicate
There is evidence consistent with sodium channelopathy in the heart during sepsis. Electrocardiography amplitude is reduced during the acute phase of sepsis. One interpretation of this is that there is reduced excitability of myocardium. Alternatively, the reduction could be due to technical factors such as fluid overload during anasarca. To directly measure myocardial excitability, the authors used cecal ligation and puncture to induce sepsis in rats and measured the papillary muscle action potential using microelectrodes. Action potential amplitude was reduced and the threshold was elevated 24 hours after induction of sepsis (Rich unpublished). Reduction in the rate of action potential rise suggests that the etiology of the reduced cardiac excitability is the reduction in the sodium current. These data are consistent with an acquired sodium channelopathy in the heart that could be a contributor to the reduced contractility of the heart that occurs during sepsis.

The authors recently found that motor neuron excitability within the spinal cord is significantly reduced within 24 hours of induction of sepsis in rats. The reduction in excitability is not apparent during stimulation of single action potentials, but becomes manifest during repetitive firing of action potentials. As motor neurons are the final common pathway through which the central nervous system (CNS) encodes muscle force and its gradation, any reduction in motor neuron excitability will reduce motor unit recruitment and contribute to weakness. Motor neurons execute their role in modulating force output by converting the synaptic current delivered to the soma into a firing rate that determines muscle force output. The finding of reduced motor neuron excitability raises the possibility that channelopathy within the CNS also contributes to weakness. Further work will be needed to determine whether reduced motor neuron excitability is due to a channelopathy distinct from the sodium channelopathy in peripheral nerve and skeletal muscle.

**SUMMARY**

Studies in skeletal muscle, peripheral nerve, heart, and spinal cord are all suggestive of an acquired channelopathy that is triggered by critical illness. No studies to date have examined excitability of neurons within the brain. Septic encephalopathy is one of the most common and troubling complications of critical illness. Despite a number of studies, the mechanism underlying septic encephalopathy remains a mystery. The presence of a channelopathy in multiple tissues raises the possibility that reduced excitability of neurons within the CNS might underlie septic encephalopathy. If this is the case, a single therapy to improve excitability might treat failure of a number of electrically active tissues.
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Rehabilitation: Prevention and Management of Neuromuscular Weakness in the Intensive Care Unit

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INTRODUCTION

Neuromuscular weakness acquired during critical illness is associated with many longterm complications after hospital discharge, including impaired physical function and decreased quality of life.1-4 Early rehabilitation in the intensive care unit (ICU) is gaining increasing recognition as an important means of reducing such complications.5 The term “early” refers to interventions that commence immediately after physiologic stabilization and often while patients remain on mechanical ventilation or vasopressor infusions.6-8 Such a focus on early rehabilitation interventions in the ICU reflects a cultural shift in care from an emphasis primarily on ICU survival to minimizing longterm morbidity.9,10

This narrative review of the literature will focus on five important aspects of early physical rehabilitation in the ICU: (1) safety, (2) feasibility, (3) benefits, (4) perceived barriers, and (5) required resources.11

SAFETY

The safety of early rehabilitation of ICU patients has been repeatedly demonstrated in clinical trials and evaluations of routine clinical care. Three independent systematic reviews, including a total of 13 studies, reported successful implementation of early rehabilitation of critically ill patients with no serious adverse events impacting patients’ survival or medical care.12-14 The most commonly cited potential safety event was transient oxygen desaturation, while accidental removal of medical devices rarely happened.15,16

Observational Studies of Safety

The physiologic effects of mobilizing ICU patients were described in a prospective study of 31 patients receiving 69 mobilization sessions in a single medical-surgical-trauma ICU.15 Of the 31 patients in the study, seven (23%) required mechanical ventilation via a tracheostomy, while the remaining were not mechanically ventilated. In 63/69 sessions (91%), patients had limited cardiopulmonary reserve prior to mobilization, as indicated by a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 or a heart rate >50% of the age-predicted maximum. Mobilization consisted of sitting on the edge of the bed with progression to standing, transferring to a chair, or walking. There was a significant increase in heart rate and blood pressure, and a nonsignificant decrease in oxygen saturation while participating in rehabilitation. Changes in patients’ physiological and clinical status warranted intervention in only 3/69 sessions (4%) during which there was a decrease in oxygen saturation requiring a temporary increase in FiO2. No life-threatening adverse events occurred.

A prospective observational pilot study of rehabilitation in the Johns Hopkins Medical ICU (MICU) also evaluated the physiologic consequences of rehabilitation.16 Heart rate, oxygen saturation, and blood pressure were recorded during 50 rehabilitation sessions in 19 patients who had been on mechanical ventilation >4 days. Changes in these physiologic markers were small and clinically unimportant.
Finally, a prospective observational evaluation of the safety of 1,449 early rehabilitation activities in 103 patients requiring mechanical ventilation >4 days in a respiratory ICU (RICU) reported that adverse events occurred in only 14 (<1%) activities. Activity events were defined as sitting on the edge of a bed or in a chair, or ambulating. For 748 activity events, patients were receiving mechanical ventilation (593 via endotracheal tube and 155 via tracheostomy). Adverse events consisted of the following: fall (five occasions), systolic blood pressure <90 mmHg (four occasions), oxygen saturation <80% (three occasions), systolic blood pressure >200 mmHg (once), and feeding tube removal (once). None of the reported events resulted in any additional therapy, prolonged length of stay (LOS), or increased hospitalization cost.

**Clinical Trials with Safety Data**

Three clinical trials of early rehabilitation demonstrated robust safety profiles. In one trial, 90 patients recruited from one medical and one surgical ICU were randomized to receive either standard rehabilitation therapy alone or standard therapy plus active training with a bedside lower extremity cycle ergometer. At the time of inclusion, 84% of patients were on mechanical ventilation. Only 16/425 (4%) of all training sessions with the cycle ergometer were stopped prematurely due to physiologic derangements with resolution always occurring within 2 min. One patient had an Achilles tendon rupture associated with cycling.

In another trial, 330 patients mechanically ventilated with an endotracheal tube were assigned to either usual care or early physical therapy delivered according to a protocol by an ICU Mobility Team consisting of a physical therapist, ICU nurse, and nursing assistant. The most common diagnosis of participants was acute respiratory distress syndrome. Of the 145 patients assigned to the intervention group, 116 (80%) had at least one physical therapy session during their hospital stay, with an average of 5.5 sessions per patient. No deaths, near-deaths, or accidental removal of devices occurred in either group.

In another controlled trial, 104 endotracheally intubated patients in two MICUs were randomly assigned to usual care or early combined physical and occupational therapy. Patients in the intervention versus control group had a significantly shorter time from intubation to first therapy session (median [interquartile range, or IQR] 1.5 days [1.0-2.1] versus 7.4 days [6.0-10.9], respectively, p<0.0001). Adverse events occurred infrequently (1/498 [0.2%] sessions) and were defined as fall to knees, endotracheal tube removal, systolic blood pressure >200 or <90 mmHg, and desaturation to <80%. Unplanned extubation or equipment removal were also recorded. There was one oxygen desaturation and one removal of a radial arterial catheter. No falls or unplanned endotracheal tube removal occurred. In 4% of all sessions, therapy was stopped prematurely due to patient instability, most commonly perceived patient–ventilator asynchrony.

**Safety of Rehabilitation with Central Venous and Arterial Catheters**

Several studies have demonstrated that early rehabilitation is safe in patients with central venous and arterial catheters. An analysis of 49 MICU patients, participating in 183 physical therapy sessions while mechanically ventilated with a central venous catheter in place, found only 1 arterial and 0 central venous catheters were inadvertently removed. The most common central venous catheter site was the internal jugular (43% of catheter-days), followed by subclavian (29%) and femoral (10%). Arterial catheters were in place for 47% of sessions.

A prospective evaluation of 101 consecutive patients with femoral catheters, conducted in the Johns Hopkins MICU, found that physical therapy sessions were safely conducted with femoral catheters in situ. The following types of femoral catheter-related events were evaluated: nonfunctioning catheter, removal of catheter, bleeding at catheter site, limb ischemia within 24 hours, retroperitoneal hematoma, and catheter line-associated blood stream infection. The most common highest daily activity levels in physical therapy sessions conducted with a femoral catheter in situ were in-bed exercises (38%), sitting (27%), standing or walking (23%), and supine cycle ergometry (12%). Venous femoral catheters were most commonly used, accounting for 71% of patient days with physical therapy in this analysis. During the study period, no femoral catheter-related adverse events occurred during rehabilitation activities (event rate: 0%; upper 95% confidence bound: 1.4%).

**Patient Safety Screening**

In order to safely engage patients in early rehabilitation, most studies and clinical programs screen patients for safety issues (e.g., cardiopulmonary instability) prior to initiation of rehabilitation interventions. The authors previously published an algorithm for evaluating patient appropriateness for active rehabilitation interventions based on review of the literature and their experiences with early rehabilitation in the Johns Hopkins MICU. Clinical judgment and interprofessional communication on the part of physicians and rehabilitation therapists is essential to determining if patients are appropriate for participation in active mobilization on a case-by-case basis.

**FEASIBILITY: THE ROLE OF INTENSIVE CARE UNIT CULTURE AND PROTOCOLS**

Early rehabilitation in an ICU is most successfully achieved through a multidisciplinary collaboration, frequently requiring a major change in ICU “culture.” ICU patients are often tethered to mechanical ventilators and devices that must be carefully managed during patient mobilization. Additionally, these patients frequently need various other diagnostic tests and therapeutic interventions that make allocating time for rehabilitation challenging. Physicians, nurses, and rehabilitation therapists must regularly communicate with each other to effectively triage patient care priorities in order to emphasize rehabilitation and successfully overcome potential logistical barriers.
A pre–post cohort study of patients requiring at least 4 days of mechanical ventilation measured the proportion of patients ambulating at 1 and 2 days before, and after, transfer from a traditional ICU to a RICU where active mobilization was a priority.\(^\text{10,23}\) The proportion of patients ambulating increased by 35% from 2 days before RICU transfer to 2 days after transfer. This increase in mobility was not explained by improved physiologic status. Notably, staffing was identical between the two ICUs, reflecting the importance of the multidisciplinary emphasis and positive “culture” supporting rehabilitation in the RICU.

Protocols and order sets may increase adherence to early engagement in rehabilitation. The previously-described clinical trial of 330 mechanically ventilated MICU patients found that implementation of an early mobility protocol, by a multidisciplinary mobility team, resulted in a greater proportion of patients in the protocol versus the usual care group receiving physical therapy during their hospital stay (80% versus 47%, \(p \leq 0.001\)).\(^\text{18}\) Of those receiving physical therapy, significantly more patients in the protocol versus the usual care group had at least one session in the ICU (91% versus 13%, \(p \leq 0.001\)). The early mobility protocol included an automatic physician order for physical therapy, rather than requiring physicians to manually place orders for individual patients in the usual care group.

A pre–post quality-improvement project, including both ICU and intermediate care patients, evaluated the effectiveness of a nurse-driven mobility protocol.\(^\text{24}\) After implementation of the protocol, there was an observed increase in ambulation from 6 to 20% of ICU patients. Another pre–post study of 100 mechanically ventilated patients in a respiratory care unit evaluated the mandatory entry of computerized mobility orders as well as a mobility protocol for nurses.\(^\text{25}\) More patients in the post-intervention versus pre-intervention group had mobility orders (82% versus 58%, \(p < 0.05\)) and were mobilized (80% versus 22%, \(p < 0.05\)). Hence, ICU culture change and the use of protocols and computerized order sets may enhance the feasibility of early rehabilitation.

**BENEFITS**

The potential benefits of early rehabilitation in the ICU include (1) improved muscle strength, functional mobility, and quality of life and (2) shorter duration of mechanical ventilation and ICU and hospital LOS which results in reduced hospitalization costs and hospital readmissions.\(^\text{5,12,13,26}\)

**Muscle Strength, Functional Mobility, and Quality of Life**

Early rehabilitation improves muscle strength, physical function, and quality of life in ICU patients.\(^\text{27-30}\) Three systematic reviews of rehabilitation in critically ill patients reported three studies that measured muscle strength using respiratory, upper limb, and/or lower limb muscle strength,\(^\text{7,12-14,32,34}\) and early rehabilitation was associated with increased muscle strength in all three studies.\(^\text{17,31,32}\) Earlier achievement of mobility milestones was noted in four studies.\(^\text{7,18,23,33}\) One randomized trial also demonstrated an association between early rehabilitation (via cycle ergometry) and improved physical function/quality of life in mechanically ventilated patients.\(^\text{17}\)

In the previously-described randomized controlled trial (RCT) of early physical and occupational therapy, patients in the intervention group were more likely to achieve the primary outcome of independent functional status at hospital discharge (59% versus 35%, \(p = 0.02\)).\(^\text{7}\) Fewer patients in the intervention group had ICU-acquired weakness as indicated by manual muscle strength testing with a Medical Research Council (MRC) score <48 (31% versus 49%, \(p = 0.09\)). While hand grip strength did not differ between groups, the intervention versus control group had a greater unassisted walking distance at hospital discharge (median [IQR] 33 m [0-91] versus 0 m [0-30], \(p = 0.004\)).

Early rehabilitation is associated with improvement in functional mobility. In the previously described prospective observational evaluation of patients requiring mechanical ventilation \(>4\) days in a RICU, patients ambulated an average of 238±191 ft on the last day of ICU admission.\(^\text{6}\) Similar results were seen in a prospective quality improvement project, including the introduction of a multidisciplinary team focused on reducing sedation and increased physical and occupational therapy staffing, in the Johns Hopkins MICU.\(^\text{33}\) The project involved 57 patients mechanically ventilated \(\geq 4\) days. A greater proportion of physical and occupational therapy treatments (56% versus 78%, \(p = 0.03\)) resulted in a functional mobility level of sitting or greater after changes in sedation and rehabilitation strategies.

**Duration of Mechanical Ventilation**

Two systematic reviews identified six studies that reported data for mechanical ventilation, and three of these studies demonstrated a significantly shorter duration of mechanical ventilation associated with physical rehabilitation.\(^\text{7,12,14,32,34}\) In the previously-described RCT of early physical and occupational therapy, patients had similar management of ICU sedation but those in the intervention versus control group had a shorter duration of mechanical ventilation (median [IQR] 3.4 days [2.3-7.3] versus 6.1 days [4.0-9.6], \(p = 0.02\)).\(^\text{7}\)

**Length of Stay and Cost Savings**

A quality improvement project in the Johns Hopkins MICU, including implementation of a multidisciplinary team approach to early rehabilitation, was associated with a decrease in average ICU LOS of 2.1 (95% CI: 0.4-3.8) days and average hospital LOS of 3.1 (0.3-5.9) days and a 20% increase in MICU admissions compared with the same period from the prior year.\(^\text{31}\)

While few studies have directly examined the association between healthcare costs and early rehabilitation, several studies suggest that early rehabilitation is associated with a reduction in costs as a result of decreased hospital and/or ICU LOS and duration of mechanical ventilation.\(^\text{7,18}\) In the above-mentioned RCT of early physical and occupational therapy, patients in the group undergoing early rehabilitation had a reduced ICU LOS (median [IQR] 5.9 days [4.5-13.2] versus 7.9 days [6.1-12.9], \(p = 0.08\)) as well as a shorter duration of mechanical ventilation (as outlined above).\(^\text{7}\) A previously described prospective cohort study of 330 MICU patients revealed a reduction in ICU and hospital LOS associated with rehabilitation according to a protocol versus usual care (mean ICU LOS 5.5 days versus 6.9 days, \(p = 0.025\);
hospital LOS 11.2 days versus 14.5 days, p=0.006). The average cost per patient also was lower in the protocol group compared with the usual care group ($41,142 versus $44,302 per patient, respectively, p=0.26). The total costs were less in the protocol group ($6,805,082) than in the usual care group ($7,309,871).

A financial model, based on existing publications and data from implementation of an early rehabilitation program in the Johns Hopkins MICU, projected that investment in early rehabilitation results in net financial savings in 20 out of a possible 24 scenarios (83%) with estimates ranging from $88,000 (net cost) to $3,763,000 (net savings).15

**PERCEIVED BARRIERS TO EARLY REHABILITATION IN THE INTENSIVE CARE UNIT**

Perceived barriers to early rehabilitation in ICU patients are commonly identified, including lack of knowledge, deep sedation, and inadequate multidisciplinary staffing.10,16,22,29 Many ICU medical and nursing staff may not fully appreciate the longterm harms of immobilization or the safety, feasibility, and benefits of early rehabilitation.8,10 Multidisciplinary education and the use of protocols to assess patient appropriateness for safe engagement in rehabilitation may address these concerns.10,22

Reducing or eliminating sedation improves participation in early rehabilitation.10,22 In a pre–post study of 104 RICU patients, the absence of sedatives was associated with increased ventilation (odds ratio [OR] 1.90; 95% CI :1.19-3.15, p=0.009).23 An observational pilot study of patients receiving mechanical ventilation >4 days in a MICU demonstrated patient sedation and/or nonresponsiveness accounted for ineligibility for rehabilitation therapy for a median (IQR) of 27% (15-61) of ICU days per patient.16 A prospective study of 514 patients in 11 ICUs found that in the 16% of patients ever receiving occupational therapy, continuous sedative infusion versus no sedative infusion was associated with a longer time to start of occupational therapy (hazard ratio=0.44, CI: 0.29-0.67).36 Use of protocols to eliminate or limit sedation and facilitate weaning has been successfully incorporated into ICU practice.22,37-40

An effective early rehabilitation program in the ICU requires collaboration among members of the multidisciplinary team. The importance of appropriate staffing for rehabilitation was demonstrated in an early pilot study in the Johns Hopkins MICU. Limited rehabilitation staffing resulted in therapy not being provided for a median (IQR) of 56% (25-68) of ICU days per patient.16

**RESOURCES FOR EARLY REHABILITATION IN THE INTENSIVE CARE UNIT**

Successful incorporation of early rehabilitation into patient care in the ICU requires contributions and collaboration from all members of the multidisciplinary team, including critical care physicians, nurses, nursing assistants, physical and occupational therapists, rehabilitation technicians, and respiratory therapists.11,22,29 In addition, having a Medical Director serving as leader for an early rehabilitation program may assist with advocating for the provision of necessary staffing and equipment.11,22

**Equipment during Ambulation**

Active early rehabilitation, especially ambulation, can prove challenging in ICU patients who may be tethered to a mechanical ventilator or other life-support devices. In order to safely facilitate mobility, appropriate equipment and trained staff may assist.11 Ambulation of a mechanically ventilated patient can be achieved using an Ambu bag with oxygen supply or a battery-powered standard ventilator. However, use of a portable ventilator may be more convenient.11 Additional helpful equipment includes a walker and/or wheelchair for balance and support, and a rolling IV pole. In order to safely ambulate a mechanically ventilated patient, two to four staff members are often needed to manage the various pieces of equipment. Devices have been proposed to simplify mobility and reduce staffing needs.41 For example, a mobility aid in use at the Johns Hopkins MICU is composed of a rolling equipment tower that includes a portable ventilator and IV pole.11,24,42

**Cycle Ergometer**

A cycle ergometer is a stationary cycling device. The ergometer can be used to passively mobilize limbs in sedated or nonresponsive patients, and it has an integrated mechanism which allows for increasing resistance for patients who are able to participate with assisted or active cycling. Cycle ergometry was associated with preserved muscle mass in immobilized healthy subjects.43 The safety and feasibility of cycle ergometry have been demonstrated in an observational study of patients during hemodialysis as well as studies evaluating bed-bound and ambulatory chronic obstructive pulmonary disease patients.44-46

An RCT of 90 critically ill patients assigned to standard physical therapy alone or standard therapy plus cycling exercises demonstrated improvement in muscle strength, physical function, and quality of life at hospital discharge in the intervention group.17 Lower extremity cycling exercises were performed with a bedside ergometer for 20 min/day, 5 days/week, in addition to standard rehabilitation therapy. Sedated or nonresponsive patients received passive cycling while awake patients actively cycled; the level of resistance was increased as tolerated for each patient. Forty-five percent of patients in the treatment group actively cycled in the first session, with an increase to 87% in the final session before ICU discharge. Although weak, there was greater improvement in quadriceps muscle force at hospital discharge in the intervention versus control group (2.4±0.6 N/kg versus 2.0±0.8 N/kg, p<0.05). Patients in the intervention group also had greater 6 minute walk distances at hospital discharge (median [IQR] 196 m [126-329] versus 143 m [37-226], p<0.05). Finally, at hospital discharge, quality of life, as measured by the SF-36 Physical Function domain, was greater in the intervention group (median [IQR] 21 [18-23] versus 15 [14-23], p<0.01).

**Neuromuscular Electrical Stimulation**

Neuromuscular electrical stimulation (NMES) therapy induces passive muscle contraction by applying electrical current to targeted muscle groups via skin electrodes.11 In healthy, immobilized volunteers, NMES was associated with preserved muscle mass.47 In an RCT of mechanically ventilated and bed-
bound chronic obstructive pulmonary disease patients, patients assigned to NMES in addition to active limb motion versus active limb motion alone had greater improvement in muscle strength (p=0.02). Studies of NMES in ICU populations show promising results. In a clinical trial of 140 critically ill patients (96% mechanically ventilated), those assigned to NMES versus standard care had a lower incidence of ICU-acquired weakness (MRC score <48) (13% versus 39%, p=0.04).22 Another RCT assigned patients who had been on mechanical ventilation for <7 days or >2 weeks to NMES or sham. While there was no difference in quadriceps muscle thickness between the NMES and sham groups, when all patients were combined for analysis, patients on mechanical ventilation for >2 weeks receiving NMES versus sham had increased quadriceps muscle thickness (+4.9% versus −3.2%, p=0.013).46 Two RCTs of patients with septic shock, in which the patients served as their own control, revealed conflicting results. The results of one of these trials applied NMES therapy to one leg and sham to the other (n=8).50 There was no difference in quadriceps muscle volume at 7 days between the two limb groups. In another trial, 16 patients received NMES and sham for 13 days using a similar design and found higher biceps and quadriceps strengths on the limb receiving NMES versus sham (p=0.005 and p=0.034, respectively). This improvement was more marked in patients with greater weakness at baseline.

**CONCLUSION**

Early rehabilitation in the ICU is safe and feasible even when performed in patients still requiring life-support therapies. The potential benefits to early rehabilitation include improved patient outcomes, such as muscle strength, functional mobility, and quality of life. Additionally, investment in an early rehabilitation program may lead to net financial savings via reduced ICU and hospital LOS and decreased duration of mechanical ventilation. A multidisciplinary team approach is favored when implementing an early rehabilitation program in the ICU in order to overcome barriers, such as over-sedation, and achieve successful change in ICU culture.

**REFERENCES**


Acquired Neuromuscular Weakness in Critical Illness

CME Questions:

1. In patients with severe sepsis and coma (septic encephalopathy) in the ICU, the approximate percent that will develop critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM) is:
   A. 5-10%.
   B. > 99%.
   C. < 1%.
   D. 90-95%.
   E. 33-50%.

2. Potential risk factors for acquired neuromuscular weakness (CIP and/or CIM) in the ICU include all the following EXCEPT:
   A. High doses of pancuronium or vecuronium.
   B. High doses of IV corticosteroids.
   C. Systemic inflammatory response syndrome (SIRS).
   D. Presence of sepsis.
   E. Known history of diabetic polyneuropathy.

3. The disorder(s) that produces the highest likelihood of developing CIP and/or CIM is:
   A. SIRS.
   B. High-dose corticosteroids.
   C. Sepsis and a high APACHE III score.
   D. Aminoglycosides.
   E. Use of non-depolarizing neuromuscular blocking agents.

4. CIP may be difficult to differentiate from CIM for the following reason(s):
   A. They both may produce profound limb weakness.
   B. They both may produce reduced CMAP amplitudes.
   C. They both may cause failure to wean from mechanical ventilation.
   D. They both may produce fibrillation potentials on EMG examination.
   E. All of the above.

5. The pathophysiologic mechanism that is most likely to result in residual weakness in a patient with CIP and CIM is:
   A. Electrical inexcitability of the muscle membrane in CIM.
   B. Loss of myosin in CIM.
   C. Septic encephalopathy associated with these disorders.
   D. Marked axonal loss in CIP.
   E. Deconditioning in a prolonged ICU stay.

6. Weakness in patients related to critical illness can be encountered in:
   A. Intensive care units.
   B. General hospital wards.
   C. EMG and outpatient clinics.
   D. Rehabilitation facilities.
   E. All of the above.

7. Generalized neuromuscular conditions associated with critical illness include all of the following EXCEPT:
   A. CIP.
   B. CIM.
   C. Disuse (cachectic myopathy).
   D. Channelopathies.
   E. Neuromuscular transmission defect.

8. Definitive diagnosis of critical illness polyneuropathy can be established in a patient with:
   A. Multiorgan dysfunction and failures.
   B. Limb weakness or difficulty weaning from the ventilator.
   C. Electrophysiologic evidence of axonal motor and sensory polyneuropathy.
   D. Absence of decremental response on repetitive nerve stimulation.
   E. All of the above.

9. The following electrophysiologic finding helps distinguish CIM from CIP on nerve conduction studies:
   A. Drop in amplitude in the compound muscle action potential (CMAP).
   B. Increased duration of CMAP.
   C. Increase in the latency of sensory nerve action potential.
   D. Increase in amplitude in the CMAP.
   E. Decreased duration of CMAP.

10. The following electrophysiologic finding is found in CIM:
    A. Presence of decremental response on repetitive nerve stimulation.
    B. High amplitude, long duration motor unit action potentials on EMG.
    C. Sensory nerve action potential amplitudes less than 80% of the lower limit of normal.
    D. CMAP amplitudes less than 80% of the lower limit of normal in two or more nerves without conduction block.
    E. Demonstration of muscle excitability.

11. Which of the following is a mechanism that commonly contributes to weakness following critical illness?
    A. Hypoperfusion of skeletal muscle.
    B. Upper motor neuron dysfunction.
    C. Loss of myosin from skeletal muscle.
    D. Demyelination of peripheral nerve.
12. Which of the following statements is correct regarding development of weakness following critical illness?
   A. Patients with sepsis develop neuropathy, but not myopathy.
   B. Patients develop myopathy only after treatment with neuromuscular blocking agents and corticosteroids.
   C. The mechanisms underlying myopathy in sepsis appear to differ from those occurring in CIM.
   D. Critical illness myopathy and critical illness neuropathy often occur simultaneously.

13. Which of the following statements is most accurate regarding the mechanism underlying reduced excitability of skeletal muscle following critical illness?
   A. The mechanism underlying reduced excitability of skeletal muscle is increased inactivation of sodium channels.
   B. The mechanism underlying reduced excitability of skeletal muscle is upregulation of a second sodium channel isoform.
   C. The mechanism underlying reduced excitability of skeletal muscle is hyperpolarization of the resting potential.
   D. The mechanism underlying reduced excitability of skeletal muscle is a mutation of Nav1.4.

14. Which of the following statements regarding critical illness polyneuropathy is most accurate?
   A. Both axon degeneration and loss of nerve excitability contribute to nerve dysfunction following critical illness.
   B. Demyelination is an important contributor to nerve dysfunction following critical illness.
   C. The rapid return of nerve function in some patients following recovery from critical illness is best explained by rapid regrowth of axons.
   D. Nerve biopsies from patients with critical illness polyneuropathy identified by nerve conduction are almost always abnormal.

15. Which of the following statements regarding the role of reduced excitability in multisystem organ failure is most accurate?
   A. There is good evidence suggesting sodium channelopathy in skeletal muscle, peripheral nerve, and the brain.
   B. There is good evidence suggesting sodium channelopathy is present in skeletal muscle and peripheral nerve. Preliminary data suggests the heart and motor neurons may also have reduced excitability.
   C. There is no good evidence suggesting sodium channelopathy in any tissue.
   D. Sodium channelopathy plays an important role in muscle dysfunction in CIM, but plays little role in nerve dysfunction in critical illness polyneuropathy.

16. When describing early rehabilitation, the term “early” refers to the initiation of rehabilitation activities:
   A. Before ICU discharge.
   B. Immediately after stabilization of physiologic derangements.
   C. After liberation from mechanical ventilation.
   D. Within seven days of ICU admission.

17. Which of the following will definitely prevent patient participation in active rehabilitation activities?
   A. Mechanical ventilation via an endotracheal tube.
   B. Continuous low-dose vasopressor infusion.
   C. Deep sedation with no response to verbal stimulation.
   D. All of the above.

18. In a study of 104 patients who required mechanical ventilation for > 4 days for respiratory failure, intrahospital transfer from a traditional ICU to a respiratory ICU focused on early mobility resulted in a 35% increase in the proportion of patients ambulating. This significant increase was largely attributed to:
   A. Protocol requiring daily interruption of continuous infusion of sedatives in the respiratory ICU.
   B. Significant improvement in patients’ physiologic status after transfer to the respiratory ICU.
   C. Increase in the staff available to assist with mobilization activities in the respiratory ICU.
   D. An ICU “culture” supporting mobilization for mechanically ventilated patients in the respiratory ICU.

19. In the studies published to date evaluating the safety of early rehabilitation and mobilization, what proportion of mechanically ventilated patients was extubated accidentally?
   A. 0%.
   B. 20%.
   C. 40%.
   D. 60%.

20. Which one of the following reflects a principle that should guide the implementation of early rehabilitation into routine patient care in the ICU setting?
   A. All ICUs must be equipped with a portable ventilator and a custom-designed mobilization device.
   B. Each ICU must have one dedicated physical therapist and one dedicated technician/assistant for every three mechanically ventilated patients.
   C. A successful rehabilitation program requires contributions and collaboration from all members of the multidisciplinary team.
   D. All of the above.