ICU-Acquired Weakness and Recovery from Critical Illness

John P. Kress, M.D., and Jesse B. Hall, M.D.

WEAKNESS ACQUIRED IN THE INTENSIVE CARE UNIT (ICU) IS CAUSED BY many different pathophysiological mechanisms that are not mutually exclusive. This is not surprising, given the diverse diseases that precipitate critical illness, the drugs used during its management, and the consequences of protracted immobility. Nonetheless, conceptualization of this entity is valuable, since weakness in survivors of critical illness is common and is associated with long-standing consequences that dramatically affect recovery. Moreover, as survival rates among patients in the ICU increase, ICU-acquired weakness will have increasing relevance for care providers outside the ICU. This article provides an overview of the condition and its effect on recovery after critical illness.

Early descriptions of weakness in critical illness include reports by Osler of neuromuscular dysfunction in patients with sepsis and reports by Olsen of peripheral neuropathy complicating protracted coma. In 1977, myopathy was described in a patient with status asthmaticus who received high doses of hydrocortisone and simultaneous neuromuscular blockade.

These descriptions were followed by a landmark study by Bolton and colleagues of polynuearopathy in patients in the ICU. This condition, termed critical illness polyneuropathy, is characterized by a primary axonal degeneration, without demyelination, that typically affects motor nerves more than sensory nerves. The predominant spinal cord finding is loss of anterior horn cells due to axonal degeneration. Electrophysiological studies show that nerve conduction velocity is preserved, but there are reductions in the amplitudes of compound muscle action potentials (CMAPs) and sensory-nerve action potentials. Over the past two decades, improvements in survival after discharge from the ICU probably have led to increased awareness of ICU-acquired weakness. The magnitude of neuromuscular impairment in the increasing population of patients undergoing post-ICU rehabilitation has come to the attention of health care providers, patients, and families.

FEATURES OF ICU-ACQUIRED WEAKNESS

Critical illness polynuearopathy affects the limbs (particularly the lower extremities) in a symmetric pattern. Weakness is most notable in proximal neuromuscular areas (e.g., the shoulders and hip girdle). In addition, involvement of the respiratory muscles can occur and can impede weaning from mechanical ventilation. Facial and ocular muscles are rarely involved. Creatine kinase levels are not elevated in patients with critical illness polyneuropathy. The condition is distinct from the Guillain–Barré syndrome because demyelination is not seen.

As distinct from a secondary myopathy resulting from muscle denervation, critical illness myopathy is a primary myopathy. It is often difficult to distinguish this myopathy from critical illness polyneuropathy by means of a simple bedside
examination. Both conditions are manifested by limb and respiratory-muscle weakness and retained sensory function; however, because altered mental status is common in patients in the ICU, sensory examination may be difficult to perform. In patients with critical illness myopathy, electrophysiological studies show reduced amplitude and increased duration of CMAPs. Histopathological analysis shows selective loss of thick filaments in muscle, which reflects myosin loss as well as muscle necrosis. Creatine kinase levels may be mildly elevated, except that in occasional cases of necrotizing myopathy, such levels are markedly elevated.

Though it is tempting to categorize weakness after recovery from critical illness as either myopathy or neuropathy, there is evidence of overlap between these pathophysiological processes. Critical illness myopathy occurs more frequently than critical illness neuropathy, and it is associated with a higher rate of recovery. Furthermore, although specific polyneuropathies, myopathies, or both contribute to physical dysfunction in critically ill patients, other variables, such as drug effects (e.g., from the use of glucocorticoids or neuromuscular blocking agents), metabolic effects (e.g., hyperglycemia), joint contractures, and muscle wasting from catabolism and physical inactivity also contribute to ICU-acquired weakness. Table 1 lists the electrophysiological features of ICU-acquired weakness.

### Table 1. Electrophysiological Features of ICU-Acquired Weakness.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Critical Illness Polyneuropathy</th>
<th>Critical Illness Myopathy</th>
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</thead>
<tbody>
<tr>
<td>Normal to minimally reduced nerve conduction velocity</td>
<td>Reduced CMAP amplitude</td>
<td>Normal to minimally reduced nerve conduction velocity</td>
</tr>
<tr>
<td>Reduced CMAP amplitude</td>
<td>Reduced compound SNAP amplitude</td>
<td>Reduced CMAP amplitude</td>
</tr>
<tr>
<td>Reduced muscle excitability on direct stimulation</td>
<td>Increased CMAP duration</td>
<td>Reduced muscle excitability on direct stimulation</td>
</tr>
<tr>
<td>Normal SNAP</td>
<td></td>
<td>Normal SNAP</td>
</tr>
</tbody>
</table>

* CMAP denotes compound muscle action potential, and SNAP sensory-nerve action potential.

The diagnosis of ICU-acquired weakness is made with the use of the Medical Research Council (MRC) scale for grading the strength of various muscle groups in the upper and lower extremities. The scale ranges from 0 to 5, with higher scores indicating greater muscle strength; a combined score of less than 48 is diagnostic of ICU-acquired weakness. Patients with ICU-acquired weakness according to the MRC examination should undergo serial evaluations, and if persistent deficits are noted, electrophysiological studies, muscle biopsy, or both are warranted. Patients with persistent coma after discontinuation of sedation should undergo studies of the central nervous system such as cranial computed tomography or magnetic resonance imaging. If such studies are normal, electrophysiological...
The pathophysiological mechanisms of ICU-acquired weakness are believed to be multifactorial. In critical illness polyneuropathy, there is speculation that a dysfunctional microcirculation leads to neuronal injury and axonal degeneration. Supporting this notion is the observation that patients with critical illness polyneuropathy have E-selectin expression in the peripheral-nerve vascular endothelium, which suggests endothelial-cell activation as described in models of sepsis, with microvascular leak and alterations in the microvascular environment. Hyperglycemia may exacerbate this problem, perhaps by inducing neural mitochondrial dysfunction. Indeed, there is evidence that aggressive glucose control may reduce the risk of critical illness polyneuropathy (and myopathy) and result in a decreased need for prolonged mechanical ventilation. However, because of the increased risk of adverse events associated with aggressive glucose control, it is not recommended solely for the prevention of critical illness polyneuropathy.

Rich and Pinter suggest that inactivation of sodium channels may contribute to critical illness–related neuropathy, myopathy, or both. They reported changes in fast sodium channels leading to inexcitability of muscle fibers in an animal model of critical illness myopathy. The same investigators reported electrocardiographic abnormalities, including decreased QRS amplitudes and increased QRS duration, in patients who recovered from septic shock; in patients who recovered from septic shock, the electrocardiographic findings returned to normal. These observations, which are consistent with the notion of a channelopathy, are intriguing because of the strong association between severe sepsis and ICU-acquired weakness.

Other conditions that are generic to the ICU may adversely affect the peripheral nervous system. A catabolic state with skeletal-muscle wasting is common and occurs rapidly in critically ill patients, particularly those with sepsis. Greater mitochondrial dysfunction has been observed in the skeletal muscle of patients who died from critical illness than in that of survivors of critical illness. Systemic inflammation and oxidative stress are associated with reduced muscle strength. Diaphragm wasting, which has been extensively described in animal models of full

### Table 2. Diseases and Syndromes Causing Weakness in Patients in the ICU.

<table>
<thead>
<tr>
<th>Condition and Pathogenesis</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillain–Barré syndrome</td>
<td>Diarrheal prodrome (e.g., <em>Campylobacter jejuni</em> infection)</td>
</tr>
<tr>
<td>Autoimmune mechanism</td>
<td>Autonomic instability, ascending paralysis, ventilatory failure</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Bulbar palsy</td>
</tr>
<tr>
<td>Antibodies against neuromuscular junction</td>
<td>Ventilatory failure</td>
</tr>
<tr>
<td>Porphyrin accumulation with resulting nerve toxicity</td>
<td>Motor axonal neuropathy, autonomic instability, abdominal pain, psychiatric manifestations</td>
</tr>
<tr>
<td>Eaton–Lambert syndrome</td>
<td>Proximal weakness</td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td>Weakness</td>
</tr>
<tr>
<td>Presynaptic calcium-channel antibodies</td>
<td>Autonomic instability</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Bulbar involvement, fasciculations, muscle atrophy</td>
</tr>
<tr>
<td>Upper and lower motor-neuron degeneration</td>
<td>Paresthesia, numbness, pain, weakness</td>
</tr>
<tr>
<td>Vasculitic neuropathy</td>
<td>Paresthesia, numbness, pain, weakness</td>
</tr>
<tr>
<td>Occlusion of vasa nervorum vessels</td>
<td>Distal polyneuropathy</td>
</tr>
<tr>
<td>Cell and immune-complex mediated</td>
<td></td>
</tr>
<tr>
<td>Cervical myelopathy</td>
<td></td>
</tr>
<tr>
<td>Mechanical injury to cervical spinal cord</td>
<td></td>
</tr>
<tr>
<td>Botulism</td>
<td>Bowel dysfunction, bladder dysfunction, or both, inhibition of acetylcholine release from presynaptic membrane, bulbar palsy, descending paralysis, autonomic dysfunction</td>
</tr>
</tbody>
</table>

studies, a muscle biopsy, or both should be performed. The MRC scale has important limitations, such as poor discrimination and a potential ceiling effect. Better bedside tools are needed to more precisely identify the presence of ICU-acquired weakness. Of course, weakness can have a broad differential diagnosis. A detailed review of specific diseases leading to weakness in patients in the ICU is beyond the scope of this article. Table 2 summarizes common diseases that cause weakness in these patients, and Figure 1 shows a diagnostic algorithm for the evaluation of weakness in critically ill patients.
mechanical ventilation,\textsuperscript{31} has also been described in studies in humans.\textsuperscript{32,33} In the diaphragm, mechanical ventilation is associated with increased activity of the ubiquitin–proteasome system, decreased levels of myosin heavy chain, and increased atrophic protein kinase B–forkhead box subgroup O (AKT-FOXO) signaling.\textsuperscript{34} Levine and colleagues\textsuperscript{32} noted atrophy in diaphragm myofibers within as

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**Figure 1. Diagnostic Algorithm for the Evaluation of Weakness in Critically Ill Patients.**

The Medical Research Council (MRC) scale grades the strength of various muscle groups in the upper and lower extremities from 0 to 5, with higher scores indicating greater muscle strength; a combined score of less than 48 is diagnostic of ICU-acquired weakness. CT denotes computed tomography, CSF cerebrospinal fluid, EEG electroencephalography, EMG electromyography, MRI magnetic resonance imaging, and NCS nerve conduction study.
system failure are important risk factors.\textsuperscript{11,37} Hyperglycemia in the ICU was reported to be an independent risk factor in one trial.\textsuperscript{13} Glucocorticoid therapy has been reported to be a risk factor in some trials.\textsuperscript{8} For instance, De Jonghe et al.\textsuperscript{11} and Herridge et al.\textsuperscript{38} reported that glucocorticoid use during an ICU stay predicted ICU-acquired weakness. Other trials have not identified glucocorticoid administration as a risk factor.\textsuperscript{22,28} In fact, Hermans et al.\textsuperscript{23} noted that glucocorticoids were associated with a protective effect with regard to ICU-acquired weakness. Despite the inconsistent findings in this area, it seems reasonable to minimize the use of glucocorticoids in patients in the ICU, given the numerous known complications associated with these drugs. Neurmuscular blocking agents used in conjunction with glucocorticoids are associated with muscle weakness in patients with status asthmaticus.\textsuperscript{3,12} However, Papazian et al.\textsuperscript{39} reported improved survival without an increase in ICU-acquired weakness with short-term use of neurmuscular blocking agents (i.e., <48 hours) in patients with a severe form of the acute respiratory distress syndrome (ARDS). The reason for these findings is not clear, though some researchers have proposed that early neuromuscular blockade may protect the diaphragm from injury due to patient–ventilator dyssynchrony.

In a study reported by De Jonghe and colleagues,\textsuperscript{11} ICU-acquired weakness was more than four times as likely to develop in women as in men. Again, the reasons for this finding are not clear, though the investigators speculated that the smaller muscle mass in women might be a predisposing factor.

There is some evidence that immobility in the ICU is associated with muscle wasting. In the conventional model of ICU care for patients with the most severe illness, patients are inactive and bedridden for a prolonged period, particularly during treatment with mechanical ventilation, and prolonged sedation and immobilization are traditionally the rule. As noted above, inactivity of

**Figure 3 (facing page). Pathophysiological Mechanisms of ICU-Acquired Weakness.**
Panel A shows skeletal-muscle wasting. Possible mechanisms include microvascular ischemia, catabolism, and immobility. Panel B shows polyneuropathy with axonal degeneration. Possible mechanisms include microvascular injury with resulting nerve ischemia, dysfunction of sodium channels, and injury to nerve mitochondria.
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Survival among patients in the ICU has improved dramatically over the past 20 years. Indeed, the observation that extremely ill patients often survive their illnesses has led to a relatively new focus of clinical investigation on patients who survive critical illness. Rehabilitation after critical illness is arduous and often frustratingly slow, particularly in elderly patients. The greatest burdens that survivors of critical illness face are related to neuromuscular dysfunction and neuropsychological maladjustment. Patients who survive respiratory failure, circulatory failure (e.g., in association with ARDS or sepsis), or both seem to have these problems with the greatest frequency and intensity. Indeed, in patients who require prolonged mechanical ventilation, neuromuscular recovery is typically prolonged and incomplete. Studies show that up to 65% of such patients have functional limitations after discharge from the hospital. Neuromuscular abnormalities may last for many years in some patients.

As mentioned earlier, in the past, routine features of general care provided in the ICU included liberal use of sedation and immobilization of the patient, which were thought to be necessary for facilitating interventions to normalize physiological function by artificial means. Recently, there has been a paradigm shift away from this approach toward a “less is more” philosophy for patients in the ICU.

This paradigm shift is consistent with the observation that long-term physical problems in survivors of critical illness, particularly those with respiratory failure, may result from the protracted ICU stay and period of immobilization during which the patient is receiving organ support that is essential for survival. Functional disability, a natural consequence of weakness, is a frequent and long-lasting complication in survivors of critical illness.

Table 3. Clinical Risk Factors and Pathophysiological Features of Critical Illness Polyneuropathy and Critical Illness Myopathy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk factors of both critical illness polyneuropathy and critical illness myopathy</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>De Jonghe et al.¹¹</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Garnacho-Montero et al.²⁸</td>
</tr>
<tr>
<td>Catabolic state</td>
<td>Trojaborg et al.,¹⁹ Garnacho-Montero et al.²⁸</td>
</tr>
<tr>
<td>Multiorgan system failure</td>
<td>De Jonghe et al.¹¹</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome</td>
<td>Jaber et al.,³³ Levine et al.²⁴</td>
</tr>
<tr>
<td>Long duration of mechanical ventilation</td>
<td>De Jonghe et al.¹¹</td>
</tr>
<tr>
<td>Immobility</td>
<td>Levine et al.,²² Papazian et al.,²⁹ Iwashyna et al.¹⁴</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Van den Berghe et al.¹³</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>De Jonghe et al.¹¹</td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td>MacFarlane and Rosenthal,³ Leatherman et al.¹²</td>
</tr>
</tbody>
</table>

Pathophysiological processes

Critical illness polyneuropathy

- Motor nerves affected more than sensory nerves: Bolton et al.⁴
- Secondary denervation muscle injury (myopathy): Bolton et al.⁹
- Proposed mechanisms:
  - Nerve ischemia: Bolton²⁰
  - Nerve microvascular injury: Bolton,²⁰ Fenzi et al.²¹
  - Nerve mitochondrial injury: Van den Berghe et al.²²
- Sodium channelopathy: Rich and Pinter²⁶

Critical illness myopathy

- Primary myopathy — selective myosin loss, muscle necrosis (e.g., ubiquitin–proteasome proteolysis): Derde et al.⁸
- Mitochondrial dysfunction: Carré et al.²⁹
- Oxidative stress: Reid and Moylan³⁰
- Sodium channelopathy: Rich and Pinter²⁶

The diaphragm is associated with rapid atrophy and dysfunction. Griffiths et al.⁴⁰ evaluated the effects of continuous passive range of motion in one leg in critically ill patients with respiratory failure who were receiving neuromuscular blockade, with the contralateral leg serving as the control. In the mobilized leg, muscle-fiber atrophy and wasting were attenuated. The clinical risk factors and pathophysiological features of critical illness polyneuropathy and myopathy are summarized in Table 3.
walk tests were still only 70% of the predicted results. Elderly survivors of critical illness appear to fare particularly poorly. Sacanella et al.47 reported a significant reduction in functional status in elderly survivors of critical illness who had normal functional status at ICU admission; functional status had not returned to baseline 1 year after discharge.

The focus on rehabilitation of critically ill patients should begin in the ICU and continue all the way to recovery at home. This is particularly important because the burden of illness affects not only the patient but his or her family or other caregivers as well. Accordingly, preparing both the patient and family or other caregivers for the difficult task of recovery may help lessen this burden.

Given the substantial physical dysfunction noted in survivors of critical illness, several investigators have evaluated the effect of ICU care that is focused on optimizing early physical activity in spite of the severity of illness. This strategy involves minimizing sedation and enlisting the early involvement of a diverse, multidisciplinary group of clinicians, including physical and occupational therapists, nurses, respiratory therapists, and patient care technicians, with the goal of getting patients up and out of bed. The discontinuation of deep sedation is a critical first step in optimizing patient activity and awareness. For example, studies have shown that the interruption of daily sedative use during mechanical ventilation increases the percentage of days during which patients are awake and able to follow commands.48 De Jonghe et al.49 noted that use of a sedation algorithm designed to allow patients to be more alert was associated with a 50% reduction in pressure sores, presumably because of reductions in sedative-related immobilization. In a before-and-after quality-improvement project, Needham et al.50 reported that changes in ICU care to reduce sedative use improved in-hospital activity levels in a group of patients in the medical ICU.

Currently, therapeutic interventions to prevent or attenuate ICU-acquired weakness and functional impairment after critical illness are limited to moderate glucose control, as noted above, and early mobilization. In 1975, Burns and Jones51 described a walker device designed for patients who require mechanical ventilation. Technological methods have evolved to the point that ambulation during mechanical ventilation44,52,53 and even extracorporeal membrane oxygenation therapy54 is now feasible. Protocols designed to mobilize patients in the ICU consist of sequential strategies from lesser to greater complexity of activities, depending on a patient’s ability to perform these activities. Such strategies are similar to the approach used by physical therapists who care for patients outside the ICU.

Bailey and colleagues52 reported on mobilization in a large cohort of patients who required mechanical ventilation. These investigators described a “culture change,” whereby activity was encouraged as soon as the condition of patients was hemodynamically stable with modest ventilator settings (i.e., fraction of inspired oxygen ≤0.6 and positive end-expiratory pressure ≤10 cm of water). Ambulation, even during mechanical ventilation, was feasible with few adverse events (e.g., device removal or deterioration of vital signs). Burtin and colleagues55 reported the benefits of a cycling exercise session with the use of a bedside cycle ergometer attached to the foot of the bed. The ergometer could provide passive range-of-motion exercise for patients who were not sufficiently alert to participate and active resistance for those who were capable of pedaling. These investigators noted improved strength and physical function at hospital discharge in the patients who were randomly assigned to cycle ergometry.

Morris et al.53 reported the results of a prospective, nonrandomized trial of mobilization in patients who were receiving mechanical ventilation. The mobilization group was out of bed faster and had shorter hospital stays. There were no differences in the duration of mechanical ventilation or in the condition of the patient at hospital discharge. At 1 year after discharge, the mobilization group was almost half as likely to have died or been rehospitalized; this suggests a better long-term recovery profile.56 In 2009, Schweickert et al.44 performed a prospective randomized, blinded trial of physical and occupational therapy from the inception of respiratory failure. This immediate mobilization strategy led to a near doubling of functional independence at hospital discharge, despite the fact that hospital length of stay did not differ between the intervention and control groups. The patients who were randomly assigned to immediate mobilization spent fewer days receiving mechanical
ventilation and had less delirium and greater maximal walking distances. In addition, more patients in the early-mobilization group were discharged to home after hospitalization. Independent predictors of functional independence at ICU discharge were younger age, absence of sepsis, and randomized assignment to early physical and occupational therapy. Despite an early, aggressive approach to mobilization in a study population that included patients with acute lung injury, morbidly obese patients, patients with shock requiring vasoactive infusions, and patients receiving ongoing renal-replacement therapy, there were very few adverse events, none of which were consequential with respect to outcome. Indeed, the most common barriers to early mobility were failure to awaken from sedation, agitation when sedation was discontinued, and scheduled diagnostic tests.  

CONCLUSIONS

Many survivors of critical illness have considerable functional impairment; a substantial contributor to such impairment is ICU-acquired weakness. Recovery is often slow and incomplete in such patients, particularly those who are elderly. Although some of the risk factors, such as sepsis, cannot necessarily be prevented, aggressive treatment of such conditions is nevertheless important to minimize subsequent morbidity. Other risk factors, such as severe hyperglycemia, can be attenuated with the use of insulin therapy with careful monitoring to avoid hypoglycemia. Early mobilization of patients in the ICU, although not a traditional approach, has become established as an evidence-based strategy to reduce the deconditioning and dysfunction so commonly seen in survivors of critical illness. For this strategy to be successful, ongoing attention to minimizing the use of sedation is important. In addition, care providers in the ICU must acknowledge the importance of a multidisciplinary care model to optimize the efficacy of early mobilization. Although preliminary data are encouraging, more research clearly is needed to determine whether the benefits of mobilizing patients in the ICU are sustained after hospital discharge.

Dr. Kress reports receiving lecture fees from Hospira and the France Foundation and fees for expert testimony in medical malpractice cases. Dr. Hall reports receiving fees for expert testimony in a patent case (Hospita v. Sandoz) and in medical malpractice cases on behalf of a patient, physicians, and hospitals. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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