

REVIEW ARTICLE

CRITICAL CARE MEDICINE

ICU-Acquired Weakness and Recovery
from Critical Illness

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

From the Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago. Address reprint requests to Dr. Kress at the University of Chicago, Department of Medicine, Section of Pulmonary and Critical Care, 5841 S. Maryland Ave., MC 6026, Chicago, IL 60637, or at jkress@medicine.bsd.uchicago.edu.

N Engl J Med 2014;370:1626-35.

DOI: 10.1056/NEJMra1209390

Copyright © 2014 Massachusetts Medical Society.

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 Osler¹ of neuromuscular dysfunction in patients with sepsis and reports by Olsen² of peripheral neuropathy complicating protracted coma. In 1977, myopathy was described in a patient with status asthmaticus³ who received high doses of hydrocortisone and simultaneous neuromuscular blockade.

These descriptions were followed by a landmark study by Bolton and colleagues⁴ of polyneuropathy 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.⁵ 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 polyneuropathy 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.⁶ 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.⁷ 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.⁸ 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.^{9,10} Critical illness myopathy occurs more frequently than critical illness neuropathy, and it is associated with a higher rate of recovery.⁹ 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 glucocorticoids¹¹ or neuromuscular blocking agents¹²), metabolic effects (e.g., hyperglycemia¹³), joint contractures,¹⁴ and muscle wasting from catabolism and physical inactivity also contribute to ICU-acquired weakness.¹⁵ Table 1 lists the electrophysiological features of ICU-acquired weakness.

DIAGNOSIS OF ICU-ACQUIRED WEAKNESS

Given the complexities of ICU-acquired weakness, a standard definition and list of nosologic features are both elusive and difficult to apply readily in clinical practice. For instance, electromyography and nerve-conduction studies are difficult to perform in many critically ill patients. The former requires that patients are awake and able to contract their muscles voluntarily; patients in the ICU are often not able to do so. Nerve-conduction studies can be confounded by problems such as tissue edema. There is controversy regarding the need — outside of research settings — to establish the diagnosis of ICU-acquired weakness on the basis of formal electrophysiological criteria.^{16,17} The nosologic scheme proposed by Stevens and colleagues¹⁸ is a reasonable classification. These investigators suggest that

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

Critical illness polyneuropathy
Normal to minimally reduced nerve conduction velocity
Reduced CMAP amplitude
Reduced compound SNAP amplitude
Critical illness myopathy
Normal to minimally reduced nerve conduction velocity
Reduced CMAP amplitude
Reduced muscle excitability on direct stimulation
Increased CMAP duration
Normal SNAP

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

the term “ICU-acquired weakness” be applied in cases in which a patient is noted to have clinically detected weakness with no plausible cause other than critical illness.

ICU-acquired weakness, with documented polyneuropathy, myopathy, or both, can be subclassified. Critical illness polyneuropathy refers to ICU-acquired weakness with electrophysiological evidence of an axonal polyneuropathy. Critical illness myopathy refers to ICU-acquired weakness with myopathy that is documented electrophysiologically or histologically. Critical illness neuromyopathy refers to electrophysiological or histologic findings of both critical illness polyneuropathy and critical illness myopathy.¹⁸

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 strength¹⁹; a combined score of less than 48 is diagnostic of ICU-acquired weakness.¹¹ 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

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

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

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.

PATHOPHYSIOLOGICAL MECHANISMS

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.²⁰ 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.²¹ Hyperglycemia may exacerbate this problem, perhaps by inducing neural mitochondrial dysfunction.²² 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.^{13,23} However, because of the increased risk of adverse events associated with aggressive glucose control,^{24,25} it is not recommended solely for the prevention of critical illness polyneuropathy.

Rich and Pinter²⁶ 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,²⁷ in patients with 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.²⁸ 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.²⁹ Systemic inflammation and oxidative stress are associated with reduced muscle strength.³⁰ Diaphragm wasting, which has been extensively described in animal models of full

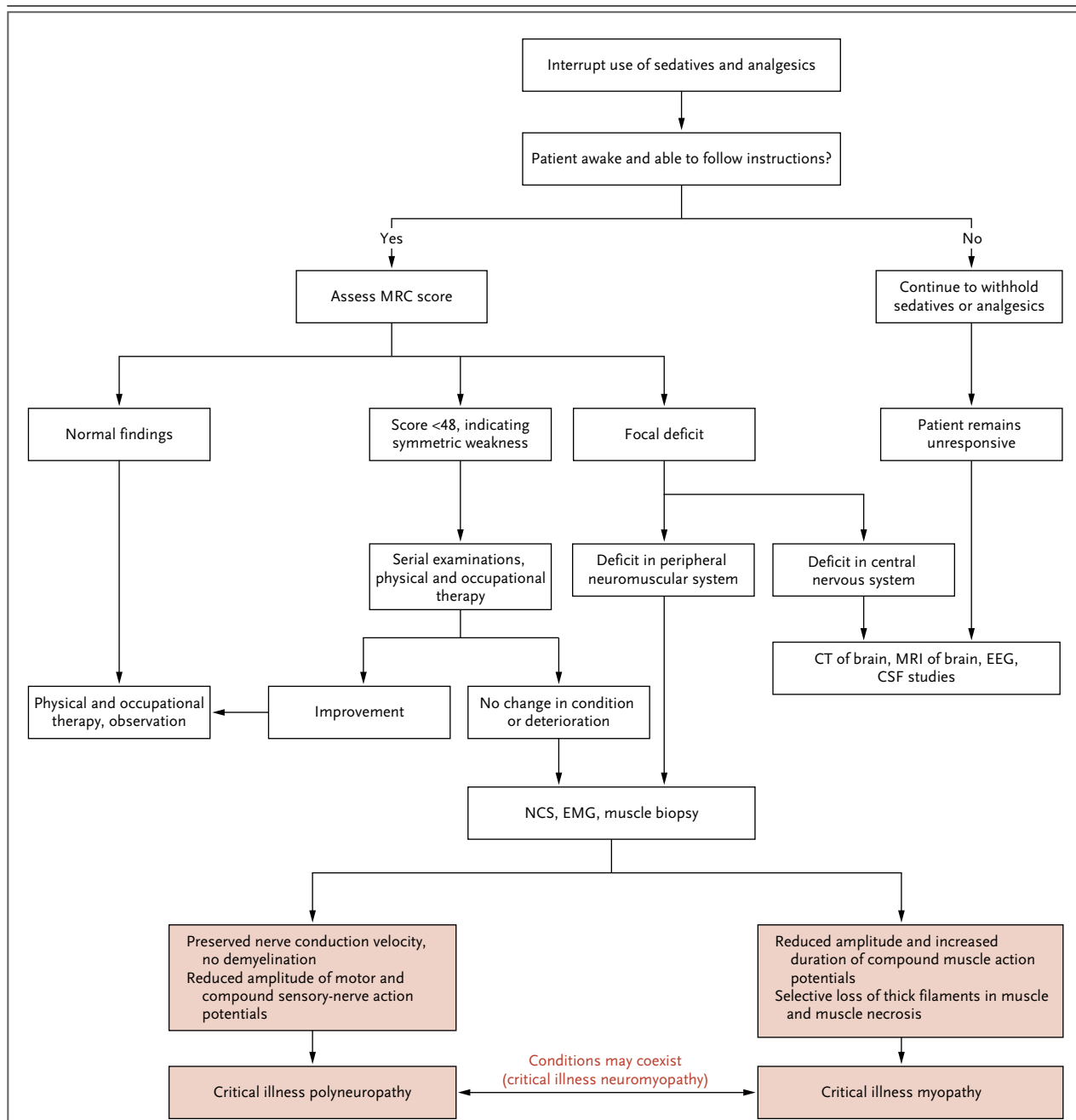


Figure 1. Diagnostic Algorithm for the Evaluation of Weakness in Critically Ill Patients.

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.

mechanical ventilation,³¹ has also been described in studies in humans.^{32,33} In the diaphragm, mechanical ventilation is associated with increased activity of the ubiquitin–proteasome system, de-

creased levels of myosin heavy chain, and increased atrophic protein kinase B–forkhead box subgroup O (AKT-FOXO) signaling.³⁴ Levine and colleagues³² noted atrophy in diaphragm myofibers within as

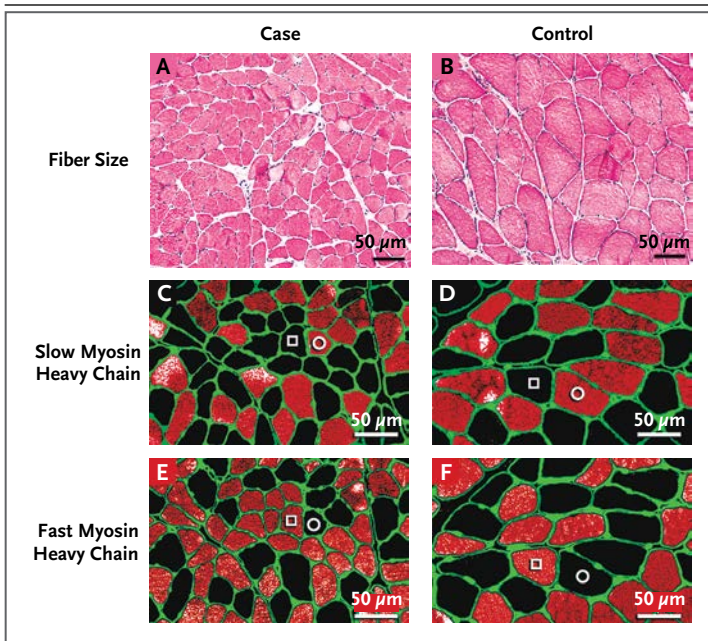


Figure 2. Changes in Fiber Size and Expression of Slow-Twitch and Fast-Twitch Myosin Heavy Chains in Patients Undergoing Mechanical Ventilation.

Shown are representative diaphragm-biopsy specimens (hematoxylin and eosin) from patients undergoing mechanical ventilation (duration of mechanical ventilation in case patients, 18 to 69 hours; duration in controls, 2 to 3 hours). As compared with diaphragm-biopsy specimens obtained from controls, specimens obtained from case patients showed smaller slow-twitch and fast-twitch fibers. Reproduced from Levine et al.³²

little as 18 hours after complete diaphragmatic inactivity in humans (Fig. 2). Jaber and colleagues³³ reported a loss of diaphragmatic strength in patients in the ICU within hours after the initiation of mechanical ventilation, which progressed over a period of 6 days of ongoing measurement. Muscle inactivity is a potent stimulus for protease activation leading to muscle protein breakdown and activation of the ubiquitin–proteasome pathway of proteolysis. Immobility of the extremities, which is common in patients in the ICU, is related to underlying illness in conjunction with prescribed bed rest and sedative-related immobility. The problems related to bed rest, including severe neuromuscular deconditioning, have been recognized for many decades.³⁵ Figure 3 shows the pathophysiological mechanisms of ICU-acquired weakness.

RISK FACTORS

The reported incidence of ICU-acquired weakness ranges from 25 to 100%.^{11,36} It is clear that sepsis, persistent systemic inflammation, and multiorgan

system failure are important risk factors.^{11,37} Hyperglycemia in the ICU was reported to be an independent risk factor in one trial.¹³ Glucocorticoid therapy has been reported to be a risk factor in some trials.⁸ For instance, De Jonghe et al.¹¹ and Herridge et al.³⁸ reported that glucocorticoid use during an ICU stay predicted ICU-acquired weakness. Other trials have not identified glucocorticoid administration as a risk factor.^{22,28} In fact, Hermans et al.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. Neuromuscular blocking agents used in conjunction with glucocorticoids are associated with muscle weakness in patients with status asthmaticus.^{3,12} However, Papazian et al.³⁹ reported improved survival without an increase in ICU-acquired weakness with short-term use of neuromuscular 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,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.

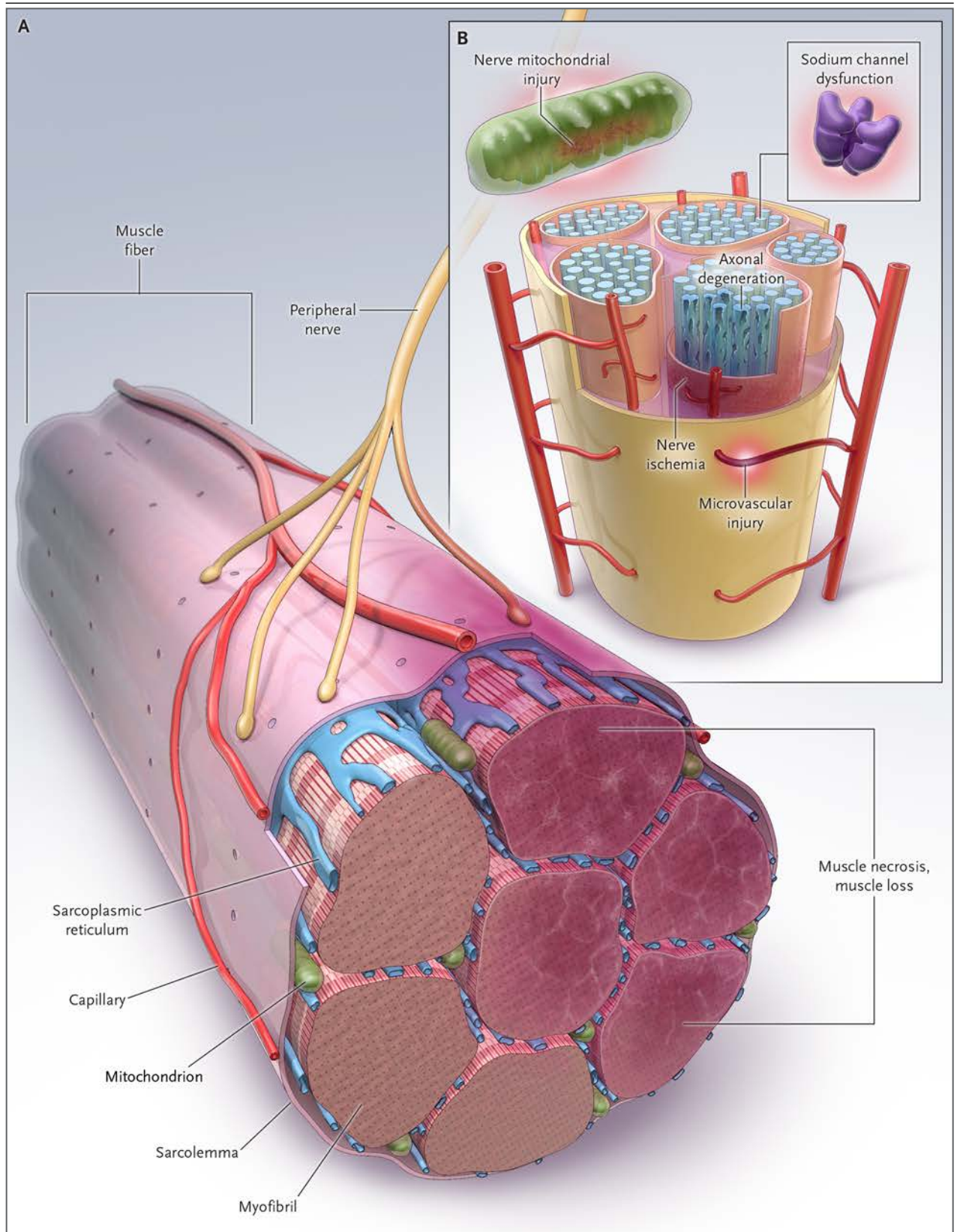


Table 3. Clinical Risk Factors and Pathophysiological Features of Critical Illness Polyneuropathy and Critical Illness Myopathy.

Variable	Reference
Clinical risk factors of both critical illness polyneuropathy and critical illness myopathy	
Female sex	De Jonghe et al. ¹¹
Sepsis	Garnacho-Montero et al. ²⁸
Catabolic state	Trojaborg et al., ¹⁵ Garnacho-Montero et al. ²⁸
Multiorgan system failure	De Jonghe et al. ¹¹
Systemic inflammatory response syndrome	Jaber et al., ³³ Levine et al. ³⁴
Long duration of mechanical ventilation	De Jonghe et al. ¹¹
Immobility	Levine et al., ³² Papazian et al., ³⁹ Iwashyna et al. ⁴¹
Hyperglycemia	Van den Berghe et al. ¹³
Glucocorticoids	De Jonghe et al. ¹¹
Neuromuscular blocking agents	MacFarlane and Rosenthal, ³ Leatherman et al. ¹²
Pathophysiological processes	
Critical illness polyneuropathy	
Motor nerves affected more than sensory nerves	Bolton et al. ⁴
Secondary denervation muscle injury (myopathy)	Bolton et al. ⁴
Proposed mechanisms	
Nerve ischemia	Bolton ²⁰
Nerve microvascular injury	Bolton, ²⁰ Fenzi et al. ²¹
Nerve mitochondrial injury	Van den Berghe et al. ²²
Sodium channelopathy	Rich and Pinter ²⁶
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 Moylan ³⁰
Sodium channelopathy	Rich and Pinter ²⁶

the diaphragm is associated with rapid atrophy and dysfunction.^{32,33} 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.

RECOVERY FROM CRITICAL ILLNESS

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.^{42,43} Patients who survive respiratory failure, circulatory failure (e.g., in association with ARDS⁴² or sepsis¹⁰), 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.^{38,44} Neuromuscular abnormalities may last for many years in some patients.⁴⁵

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.⁴⁶

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.⁴¹ Herridge et al.³⁸ followed a cohort of survivors of ARDS for 5 years after hospital discharge. Muscle weakness and functional impairment were frequently observed at 1 year, and recovery from physical dysfunction was incomplete even 5 years after discharge.⁴² At the 5-year assessment, the results of 6-minute

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 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 ventilation^{44,52,53} 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.⁵⁷

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 (*Hospira 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.

REFERENCES

- Osler W. The principles and practice of medicine, designed for the use of practitioners and students of medicine. New York: D. Appleton, 1915:114-8.
- Olsen CW. Lesions of peripheral nerves developing during coma. *JAMA* 1956;160:39-41.
- MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. *Lancet* 1977;2:615.
- Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry* 1984;47:1223-31.
- Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. *Brain* 1987;110:819-41.
- De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med* 2004;30:1117-21.
- Latronico N, Fenzi F, Recupero D, et al. Critical illness myopathy and neuropathy. *Lancet* 1996;347:1579-82.
- Derde S, Hermans G, Derese I, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. *Crit Care Med* 2012;40:79-89.
- Koch S, Spuler S, Deja M, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. *J Neurol Neurosurg Psychiatry* 2011;82:287-93.
- Latronico N. Neuromuscular alterations in the critically ill patient: critical illness myopathy, critical illness neuropathy, or both? *Intensive Care Med* 2003;29:1411-3.
- De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002;288:2859-67.
- Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med* 1996;153:1686-90.
- van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67.
- Clavet H, Hébert PC, Fergusson DA, Doucette S, Trudel G. Joint contractures in the intensive care unit: association with resource utilization and ambulatory status at discharge. *Disabil Rehabil* 2011;33:105-12.
- Trojaborg W, Weimer LH, Hays AP. Electrophysiologic studies in critical illness associated weakness: myopathy or neuropathy — a reappraisal. *Clin Neurophysiol* 2001;112:1586-93.
- Bednarik J, Lukas Z, Vondracek P. Critical illness polyneuropathy: the electrophysiological components of a complex entity. *Intensive Care Med* 2003;29:1505-14.
- Morris C, Trinder JT. Electrophysiology adds little to clinical signs in critical illness polyneuropathy and myopathy. *Crit Care Med* 2002;30:2612.
- Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* 2009;37:Suppl: S299-S308.
- Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991;14:1103-9.
- Bolton CF. Neuromuscular manifes-

- tations of critical illness. *Muscle Nerve* 2005;32:140-63.
21. Fenzi F, Latronico N, Refatti N, Rizuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol* 2003;106:75-82.
 22. Van den Berghe G, Schoonheydt K, Beccx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology* 2005;64:1348-53.
 23. Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med* 2007;175:480-9.
 24. The NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108-18.
 25. *Idem*. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97.
 26. Rich MM, Pinter MJ. Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. *J Physiol* 2003;547:555-66.
 27. Rich MM, McGarvey ML, Teener JW, Frame LH. ECG changes during septic shock. *Cardiology* 2002;97:187-96.
 28. Garnacho-Montero J, Madrazo-Osuna J, Garcia-Garmendia JL, et al. Critical illness polyneuropathy: risk factors and clinical consequences: a cohort study in septic patients. *Intensive Care Med* 2001;27:1288-96.
 29. Carré JE, Orban JC, Re L, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med* 2010;182:745-51.
 30. Reid MB, Moylan JS. Beyond atrophy: redox mechanisms of muscle dysfunction in chronic inflammatory disease. *J Physiol* 2011;589:2171-9.
 31. Powers SK, Shanely RA, Coombes JS, et al. Mechanical ventilation results in progressive contractile dysfunction in the diaphragm. *J Appl Physiol* 2002;92:1851-8.
 32. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327-35.
 33. Jaber S, Petrof BJ, Jung B, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med* 2011;183:364-71.
 34. Levine S, Biswas C, Dierov J, et al. Increased proteolysis, myosin depletion, and atrophic AKT-FOXO signaling in human diaphragm disuse. *Am J Respir Crit Care Med* 2011;183:483-90.
 35. Dock W. The evil sequelae of complete bed rest. *JAMA* 1944;125:1083-5.
 36. Bednarik J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuropathy. *J Neurol* 2005;252:343-51.
 37. Druschky A, Herkert M, Radespiel-Troger M, et al. Critical illness polyneuropathy: clinical findings and cell culture assay of neurotoxicity assessed by a prospective study. *Intensive Care Med* 2001;27:686-93.
 38. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683-93.
 39. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107-16.
 40. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, MacMillan RR. Effect of passive stretching on the wasting of muscle in the critically ill. *Nutrition* 1995;11:428-32.
 41. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010;304:1787-94.
 42. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293-304.
 43. Hopkins RO, Jackson JC. Short- and long-term cognitive outcomes in intensive care unit survivors. *Clin Chest Med* 2009;30:143-53.
 44. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009;373:1874-82.
 45. Fletcher SN, Kennedy DD, Ghosh IR, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Crit Care Med* 2003;31:1012-6.
 46. Slutsky AS. Neuromuscular blocking agents in ARDS. *N Engl J Med* 2010;363:1176-80.
 47. Sacanella E, Perez-Castejon JM, Nicolas JM, et al. Functional status and quality of life 12 months after discharge from a medical ICU in healthy elderly patients: a prospective observational study. *Crit Care Med* 2011;15(2):R105.
 48. Kress JB, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000;342:1471-7.
 49. De Jonghe B, Cook D, Griffith L, et al. Adaptation to the Intensive Care Environment (ATICE): development and validation of a new sedation assessment instrument. *Crit Care Med* 2003;31:2344-54.
 50. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a Quality Improvement Project. *Arch Phys Med Rehabil* 2010;91:536-42.
 51. Burns JR, Jones FL. Letter: Early ambulation of patients requiring ventilatory assistance. *Chest* 1975;68:608.
 52. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med* 2007;35:139-45.
 53. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238-43.
 54. Turner DA, Cheifetz IM, Rehder KJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. *Crit Care Med* 2011;39:2593-8.
 55. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009;37:2499-505.
 56. Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci* 2011;341:373-7.
 57. Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med* 2010;38:2089-94.

Copyright © 2014 Massachusetts Medical Society.

POSTING PRESENTATIONS FROM MEDICAL MEETINGS ONLINE

Online posting of an audio or video recording of an oral presentation at a medical meeting, with selected slides from the presentation, is not considered prior publication. Authors should feel free to call or send e-mail to the Journal's Editorial Offices if there are any questions about this policy.