

Intensive-Care-Unit-Acquired Muscle Weakness

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Neuromuscular abnormalities culminating in skeletal-muscle weakness occur very commonly in critically ill patients. Intensive-care-unit (ICU) acquired neuromuscular abnormalities are typically divided into 2 discrete classes: polyneuropathy and myopathy. However, it is likely that these 2 entities commonly coexist, with myopathy being the most common cause of weakness. Major risk factors for ICU-acquired neuromuscular abnormalities include sepsis, corticosteroid administration, and hyperglycemia, with other associated factors including neuromuscular blockade and increasing severity of illness. The pathogenesis of these disorders is not well defined, but probably involves inflammatory injury of nerve and/or muscle that is potentiated by functional denervation and corticosteroids. ICU-acquired neuromuscular abnormalities are associated with multiple adverse outcomes, including higher mortality, prolonged duration of mechanical ventilation, and increased length of stay. The only intervention proven to reduce the incidence of ICU-acquired neuromuscular abnormalities is intensive insulin therapy. Additional research is necessary to better delineate the causes and pathogenesis of these disorders and to identify potential preventive and therapeutic strategies. In addition, consensus guidelines for its classification and diagnosis are needed. *Key words: neuromuscular, weakness, polyneuropathy, myopathy, polyneuromyopathy, intensive care, inflammation, mechanical ventilation, insulin, critical illness.* [Respir Care 2006;51(9):1042–1052. © 2006 Daedalus Enterprises]

Introduction

Weakness that is acquired during hospitalization for critical illness is increasingly recognized as a common and

important clinical problem. Weakness acquired in the intensive care unit (ICU) and related acquired neuromuscular dysfunction occur in a large percentage of critically ill patients^{1–3} and are associated with increased morbidity and mortality.^{4,5} In addition, it is estimated that the development of ICU-acquired paresis may result in an average of \$66,000 per patient in excess hospital charges (1996

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United States dollars).⁶ This review will discuss the incidence, causes, importance, pathogenesis, diagnosis, and prevention of ICU-acquired paresis and associated ICU-acquired neuromuscular disorders.

Definitions

Because weakness in critically ill patients has been described in a variety of clinical situations and ascribed to more than one etiology, several descriptive terms have been coined to attempt to define and differentiate weakness syndromes. These include critical-illness polyneuropathy, critical-illness myopathy, and acute quadriplegic myopathy. Unfortunately, these terms may be too restrictive in that they imply a single and distinct cause of weakness for each patient or group of patients, when in fact the pathology appears to be more complex, with considerable overlap between the "syndromes." For example, myopathy appears to be present in the majority of cases that might once have been classified as polyneuropathy (discussed in detail later).^{7,8} In addition, these terms are not necessarily applied to patients with clinical evidence of weakness; for example, critical-illness polyneuropathy has been defined solely by abnormalities on electrophysiologic testing (nerve-conduction studies and electromyography [EMG]) in several studies.^{4,9-13} These factors create considerable confusion when trying to read the literature on ICU-acquired weakness. Thus, additional terms have been coined that reflect the complexity and uncertainty of the cause of ICU-acquired weakness, including "critical-illness neuromuscular abnormalities,"¹⁴ "critical illness myopathy and neuropathy,"¹⁵ "critical illness polyneuropathy and myopathy,"¹² and "critical illness polyneuromyopathy."¹⁶ Lastly, a term that refers only to the *presence* of weakness, rather than cause, was recently suggested: "ICU-acquired paresis." To reduce confusion, this review will avoid acronyms, and use the general terms "ICU-acquired weakness" and "neuromuscular abnormalities or disorders."

Incidence

Only a few studies have rigorously and systematically studied the incidence of ICU-acquired weakness. Many of the original reports on ICU-acquired neuromuscular disorders were case reports or case series of retrospectively identified patients, with no denominator available for measurement of the frequency of this problem.¹⁷⁻²¹ Several subsequent prospective studies have suggested that the incidence of weakness combined with abnormalities on nerve-conduction studies and/or EMG in patients mechanically ventilated for more than 4-7 days is very high (33-82%).^{2,3,22-26} However, these studies included patients with altered levels of consciousness, so they relied on nerve-conduction studies and EMG testing or nonrigorous defi-

nitions of weakness for diagnosis, which may have resulted in overestimation of weakness, although the presence of electrophysiologic abnormalities may be an independently important predictor of outcome.^{4,13}

Taking a different approach, De Jonghe et al prospectively identified patients who were mechanically ventilated for ≥ 7 days, and evaluated them for weakness only when they awakened and were able to cooperate with physical examination.¹ Clinically important weakness was defined as the inability to move against resistance and was quantitated using the Medical Research Council summation score of testing in 12 muscle groups (upper and lower limbs).²⁷ Ninety-five of 206 enrolled patients were evaluable during their hospitalization; of these, 25% developed severe weakness.¹ This study provides the most conservative estimate of ICU-acquired paresis, but probably underestimated the incidence of neuromuscular problems in the entire population of critically ill patients, including those who die or are transferred from the hospital before they can cooperate with a strength examination, or those with milder degrees of weakness. It is unclear how neuromuscular abnormalities contribute to morbidity and mortality in this latter group of patients.

Certain groups of patients appear to be at high risk for developing ICU-acquired neuromuscular abnormalities, undoubtedly due to the presence of specific risk factors, as discussed in a following section. In 5 prospective studies of patients with sepsis and/or septic shock, electrophysiologic abnormalities were detected in 53%, 68%, 71%, 76%, and 100% of patients, although clinical evidence of weakness was not reported in all the studies.^{4,10,11,13,28}

Berek et al prospectively evaluated 22 patients with sepsis or the systemic inflammatory response syndrome (SIRS) and multiple-organ-failure, and found electrophysiologic abnormalities in 82% of patients.²⁵ Of note, only half of these patients had clinical evidence of weakness, although clinical examination was not performed in all patients.

In another prospective study of patients with failure of ≥ 2 organs, 56% of patients developed electrophysiologic abnormalities, 52% developed some focal or diffuse weakness, and 26% developed severe diffuse weakness.⁸ Finally, in a retrospective analysis of 50 consecutive patients with acute respiratory distress syndrome and sepsis/SIRS, Bercker et al reported that 27 of 45 ICU survivors (60%) developed severe clinical weakness, with 25 patients exhibiting concomitant electrophysiologic abnormalities.²⁹ Thus, sepsis, SIRS, and multiple-organ-failure appear to place patients at considerable risk for ICU-acquired neuromuscular disorders.

ICU-acquired weakness is generally reported in patients who have been mechanically ventilated for ≥ 7 days. However, there is evidence that nerve and/or muscle injury may begin early in the course of hospitalization, particularly in

high-risk patients. Electrophysiologic testing (nerve-conduction studies/EMG) of 9 patients with sepsis or SIRS who were in the ICU for 2–7 days (mean 3.9 d) found evidence of neuromuscular abnormalities in all.¹⁰ Strength testing was not reported in that study.

In another study of 25 patients with septic shock, 50% had developed diffuse weakness within 72 hours of diagnosis, and 68% had concomitant electrophysiologic evidence of critical-illness polyneuropathy.²⁸ Thus, although the risk of an ICU-acquired neuromuscular disorder appears to increase with the duration of critical illness, abnormalities begin to develop early in the hospital course, and it appears that the vast majority of patients admitted to the ICU with sepsis will exhibit electrophysiologic neuromuscular abnormalities by day 10 of their ICU stay.^{4,28}

In patients with severe acute asthma undergoing mechanical ventilation, 2 retrospective studies reported the incidence of weakness attributed to myopathy at 10% and 18%.^{30,31} However, a small, prospective trial found a much higher incidence of clinically important weakness in patients with severe acute asthma (36%).³² Similar findings were reported in patients undergoing mechanical ventilation and receiving corticosteroids for exacerbations of chronic obstructive pulmonary disease.³³ The high incidence of myopathy in these latter 2 studies probably reflects the higher identification of cases when systematic examination and reporting are used.

Pathology of ICU-Acquired Weakness

ICU-acquired weakness has been attributed to several underlying pathologies, although it is unclear if there are in fact multiple distinct entities or, rather, one disease with variable presentations. The major categories of ICU-acquired neuromuscular dysfunction grew from descriptions of myopathy^{21,34} and then polyneuropathy²⁰ in the 1970s and 1980s. These categories and the case for their shared features will be discussed in the following section.

So-called “acute quadriplegic myopathy” was originally and has frequently since been reported in patients with severe acute asthma who were receiving high-dose corticosteroids and/or neuromuscular blocking agents.^{21,32,35–41} However, acute quadriplegic myopathy has also been reported in association with a variety of critical illnesses, including acute respiratory distress syndrome, sepsis, and after heart, lung, and liver transplantation.^{34,42–48} Frequently, but not always, corticosteroids and neuromuscular blocking agents were implicated in the cause of these cases (discussed in detail later).

Two major pathologic patterns have been described in muscle-biopsy specimens from patients with ICU-acquired myopathy. One variant is described as selective thick (myosin) filament loss under electron microscopy, with generalized or selective Type II fiber atrophy on light micros-

copy.^{1,33–35,48,49} The second variant presents as widespread muscle necrosis with vacuolization and phagocytosis of muscle fibers.^{31,42,43,50,51} Inflammatory infiltration has been described in some cases.⁵² Acute necrotizing myopathy has been associated with renal failure and may be related to reports of rhabdomyolysis in patients with severe acute asthma.^{51,53,54} Atrophy, thick-filament loss, and necrosis have been described in single biopsy specimens, suggesting that there may be a spectrum of injury between these variants.^{1,55,56} The risk factors and recovery pattern of these 2 variants do not appear to differ.

Critical-illness polyneuropathy was originally and is most frequently described in patients with sepsis, SIRS, and multiple-organ-failure.^{18,20,23,26,57,58} However, motor neuropathy has also been described in patients with respiratory failure due to asthma.⁵⁹ The presentation is similar to acute quadriplegic myopathy, with diffuse weakness. The diagnosis has typically been made by electrophysiologic testing, with nerve-conduction studies revealing reduced motor and often sensory nerve action potentials, and muscle fibrillation on EMG that is suggestive of denervation.^{20,58} Critical-illness polyneuropathy can be distinguished from demyelinating diseases such as Guillain-Barré syndrome by the preservation of nerve-conduction velocity.⁵⁸ Nerve biopsies in some studies have shown axonal degeneration,^{18,56,60} although in others no abnormalities were evident.^{49,61} However, nerve biopsies are rarely performed or reported. Until very recently, critical-illness polyneuropathy was thought to be the major cause of ICU-acquired weakness.⁶²

The simultaneous presence of critical-illness polyneuropathy and myopathy has been described for many years.^{15,16,24} However, the impracticality and infrequency of muscle biopsy in many studies of ICU-acquired neuromuscular disorders have probably resulted in an underestimation of the incidence of myopathy. Several studies in which muscle biopsies were performed found a high frequency of myopathic changes in unselected patients, in those evaluated for weakness, and in patients with electrophysiologic evidence of neuropathy.^{1,24,42,49,61} In a study by De Jonghe et al of ICU-acquired weakness, 22 patients underwent electrophysiologic testing, and all had evidence of sensory and motor neuropathy. However, muscle biopsies from ten of those patients revealed primary myopathy.¹ In a recent prospective study of 15 patients who underwent electrophysiologic testing and nerve and muscle biopsy for evaluation of ICU-acquired weakness, 13/15 patients had myopathic changes in the form of muscle necrosis and/or myosin loss; the other two had muscle atrophy.⁵⁶ Seven patients also had evidence of axonal degeneration; however, only 2 patients appeared to have neuropathy as the primary cause of weakness.

This infrequency of muscle biopsies is compounded by the imprecision of standard electrophysiologic studies

(nerve-conduction studies and EMG) in distinguishing between motor neuropathy and myopathy in critically ill patients who cannot cooperate with testing by voluntarily contracting muscles.⁶³ Direct stimulation of muscle may overcome this inherent limitation of standard EMG, in that myopathic muscle shows reduced excitability, compared to normal or atrophied muscle.⁶⁴ Studies that used direct muscle stimulation revealed a predominance of myopathic changes in patients with ICU-acquired weakness, whereas standard nerve-conduction studies and EMG may have led to a diagnosis of polyneuropathy in many of these patients.^{61,64,65} Thus, myopathy may be the primary or a contributing factor in a large percentage of patients with ICU-acquired weakness. Moreover, it has become increasingly apparent that neuropathy and myopathy are probably interrelated “organ” dysfunctions related to SIRS, and potentiated by other risk factors such as corticosteroids, as will be discussed in the next section. The relative contributions of polyneuropathy and myopathy to ICU-acquired weakness are difficult to ascertain.

Risk Factors and Pathogenesis

As noted previously, sepsis and SIRS appear to be important risk factors for the development of ICU-acquired weakness. In addition to the previously discussed high incidence of ICU-acquired neuromuscular disorders in patients with sepsis, several prospective studies of mechanically ventilated, critically ill patients have identified sepsis as an important risk factor.^{12,23,33} In a prospective evaluation of a mixed population of 98 critically ill patients, 33% of whom developed neuromuscular disorders while in the ICU, SIRS and severity of illness (as assessed with the Acute Physiology and Chronic Health Evaluation [APACHE III]) were identified as the only independent risk factors for the development of neuromuscular abnormalities.² On the other hand, not all studies have found an independent association between sepsis and neuromuscular abnormalities in the ICU, which reflects the complexity of the pathogenesis of this problem.^{1,3}

It has been proposed that ICU-acquired neuromuscular abnormalities are an “organ failure” caused by inflammatory mediators that are either systemically or locally produced in sepsis and SIRS.^{66,67} Analysis of muscle specimens from patients with ICU-acquired neuromuscular abnormalities reveals macrophage and T-cell infiltration and expression of both pro- and anti-inflammatory cytokines.⁵² Furthermore, muscle from septic patients exhibits over-expression of other pro- and anti-inflammatory enzymes and activation of a key intracellular proteolytic pathway (ubiquitin-proteasome).^{68,69} Animal models of sepsis confirm the presence of increased muscle proteolysis related to the ubiquitin-proteasome pathway, which is further activated by corticosteroids.^{68,70,71} Lastly, serum from

patients with sepsis and/or neuromuscular abnormalities exhibits neurotoxicity and effects on muscle membrane excitability and intracellular calcium release that could contribute to clinical neuromuscular abnormalities.^{72,73} The nature of the circulating mediator or mediators is not clear; tumor necrosis factor has been suggested as a likely culprit,^{74,75} although one study found no evidence of elevated tumor necrosis factor or interleukin-6 in the serum of patients with critical-illness polyneuropathy.⁷⁶ However, in that study, tumor necrosis factor was measured after the established diagnosis of polyneuropathy, whereas peak levels and nerve or muscle injury probably occurred earlier in the course of illness.

Corticosteroid administration is another commonly identified risk factor for ICU-acquired weakness. ICU-acquired myopathy has been frequently described in asthmatics and other patients who received high-dose corticosteroids, often in association with other potential risk factors, such as sepsis or neuromuscular blockade.^{21,30,31,33–37,39,46,48,50,55,59,77} In a prospective study of critically ill patients, De Jonghe et al found that corticosteroid administration was the strongest predictor of ICU-acquired weakness (odds ratio 14.9, 95% confidence interval 3.2–69.8).¹ However, ICU-acquired weakness, myopathy, and polyneuropathy have also been described in the absence of corticosteroid administration, which once again emphasizes our incomplete understanding of this syndrome.^{2,29,44}

The third major risk factor associated with ICU-acquired weakness is the administration of neuromuscular blocking drugs. Many of the early reports of ICU-acquired myopathy in asthmatics and other patients with respiratory failure in the 1970s, 1980s, and early 1990s occurred at a time when it was common practice to administer neuromuscular blocking drugs to facilitate mechanical ventilation. Because these patients often received both corticosteroids and neuromuscular blocking drugs, it is difficult to distinguish the respective roles these agents played in the development of myopathy.^{41,50} However, several studies showed that neuromuscular blockade was clearly associated with increased risk of myopathy, particularly as the duration of drug administration increased beyond 24 hours.^{30,31,78,79} The enthusiasm for neuromuscular blockade in the ICU diminished considerably after the relationship to myopathy became clear. Despite this, ICU-acquired neuromuscular abnormalities continue to occur with alarming frequency, and several recent studies found no relationship between ICU-acquired weakness and neuromuscular blockade.^{1,2,29,33,44}

The interaction between corticosteroids, neuromuscular blockade, and ICU-acquired neuromuscular abnormalities may be explained by the observation that denervation increases steroid-receptor density in muscle.⁸⁰ Administration of corticosteroids to animals with denervated muscle

results in thick-filament (myosin) loss, similar to that seen in patients with ICU-acquired myopathy.⁸¹ Furthermore, denervated muscle in animals treated with corticosteroids loses membrane excitability, again similar to that seen in patients with ICU-acquired myopathy.^{64,82} This loss of membrane excitability may be due to inactivation of membrane sodium channels.⁸³ Thus, it is likely that neuromuscular blockade functionally “denervates” muscle, thereby potentiating the direct muscle toxicity of corticosteroids. A direct toxic effect of neuromuscular blocking agents has not been established.

It was originally proposed that the type of neuromuscular blocking drug was related to the development of myopathy, and that the aminosteroid agents vecuronium and pancuronium were particularly harmful.⁷⁸ However, there have since been many reports of myopathy developing after the use of structurally unrelated neuromuscular blocking drugs (atracurium, cisatracurium, and doxacurium),^{31,84–90} which suggests that the earlier reports were related to the more frequent use of vecuronium and pancuronium rather than to their specific toxic effect.

Prolonged neuromuscular blockade after discontinuation of the drugs can also present as prolonged weakness in the ICU.^{19,91,92} This is more likely to occur with the use of vecuronium or pancuronium, particularly to patients with renal insufficiency, given that these agents and their active metabolites are cleared by the kidney.⁹² Prolonged neuromuscular blockade can be distinguished from other causes of ICU-acquired neuromuscular abnormalities by documentation of fade on repeated peripheral motor-nerve stimulation (train-of-4), or by evidence of a neuromuscular transmission defect on formal electrophysiologic testing. Prolonged neuromuscular blockade can be minimized by careful titration and monitoring of these drugs, and the use of non-renally-cleared agents, such as cisatracurium, in patients with renal insufficiency.

Several retrospective and prospective studies have identified hyperglycemia as a fourth major risk factor for the development of ICU-acquired neuromuscular disorders.^{1,22,29,93} It is not clear whether hyperglycemia is a truly independent risk factor or merely associated with others, such as sepsis or glucocorticoid administration. However, a large, prospective trial of tight glycemic control using intensive insulin therapy in critically ill surgical patients dramatically reduced electrophysiologically diagnosed polyneuropathy.⁹ In post-hoc analysis of that trial, the level of glycemic control (as opposed to other metabolic effects of insulin) appeared to account for the reduction in polyneuropathy.^{93,94}

The mechanism by which hyperglycemia leads to muscle and/or nerve injury is at this point unknown. There is some evidence that aggressive glycemic control protects hepatocytes from mitochondrial injury;⁹⁵ it is possible that hyperglycemia potentiates the mitochondrial dysfunction

of sepsis, thus leading to or exacerbating injury in multiple organs, including muscle and nerves.⁹⁶ In addition, insulin increases mitochondrial adenosine-triphosphate production and protein synthesis in skeletal muscle, counteracting the effect of corticosteroids in this regard.^{97,98} This may provide some explanation for the protective effect of intensive insulin therapy observed by Van den Berghe et al.^{93,94} However, further research is needed to elucidate the role that hyperglycemia plays in the development of ICU-acquired neuromuscular abnormalities.

Additional but less consistently identified risk factors for ICU-acquired neuromuscular abnormalities include administration of total parenteral nutrition, aminoglycosides, catecholamines, hyperosmolality, neurologic failure, female sex, greater quantity and longer duration of organ dysfunction, and greater severity of illness.^{1,2,4,12,23,33,73} Renal failure has been reported as a risk factor,²⁶ whereas renal-replacement therapy has been reported as protective.⁴

In summary, the major identified risk factors for ICU-acquired neuromuscular abnormalities include sepsis/SIRS, corticosteroids and neuromuscular blocking drugs, and hyperglycemia. Experimental models and testing of muscle samples from patients with sepsis or myopathy provide some insight into the mechanisms by which muscle injury occurs in critical illness, but the pathogenesis of nerve injury remains unknown. Friedrich et al summarized the pathogenic factors leading to critical-illness myopathy as “predisposing” factors such as sepsis or SIRS, “priming” factors such as denervation (eg, neuromuscular blockade), and “triggering” factors such as corticosteroids.⁶⁷ This model may well be applied to the entire spectrum of ICU-acquired neuromuscular abnormalities and may involve other predisposing factors such as genetics, and triggering factors such as hyperglycemia, renal failure, and others. In the right combination, these factors lead to a syndrome of weakness that is associated with poor outcome, as will be described in the next section.

Clinical Presentation and Outcomes

ICU-acquired neuromuscular disorders generally present as diffuse skeletal-muscle weakness, unless diagnosed by electrophysiologic testing, as in the context of a research study. Muscles are generally flaccid and deep-tendon reflexes absent, although spastic quadriplegia and isolated limb weakness have also been described.^{8,32,99} It is also likely that a common initial presentation is failure to separate from mechanical ventilation, given the evidence that ICU-acquired neuromuscular disorders affect respiratory as well as skeletal muscles. Spitzer et al found that 62% of patients with prolonged ventilator dependence in association with critical illness had a possible neuromuscular cause of ventilatory failure, including critical-illness polyneu-

ropathy and/or myopathy.⁵ Several studies have found abnormal phrenic-nerve and/or diaphragm function by electrophysiology in the presence of ICU-acquired neuromuscular disorders.^{18,22,45,100,101} In addition, several prospective studies have found that ICU-acquired neuromuscular disorders are associated with longer duration of mechanical ventilation and length of stay,^{1,4,12,13,23,32,33} although cause-and-effect cannot be proven, given that the severity of illness and neuromuscular abnormalities are linked. ICU-acquired neuromuscular abnormalities have also been implicated in respiratory failure that develops after discharge from the ICU.¹⁰²

Three studies are of particular interest in regard to the association between ICU-acquired neuromuscular disorders and prolonged mechanical ventilation. In their (above-described) prospective study, De Jonghe et al¹ found that the presence of ICU-acquired weakness by clinical examination was associated with more than twice the mean duration of mechanical ventilation (compared to controls without weakness) after patient awakening (18.2 ± 36.3 d vs 7.6 ± 19.2 d, $p = 0.03$). There was also a trend toward longer ICU stay for patients with weakness (27.6 ± 31.4 d vs 14.6 ± 19.6 d, $p = 0.06$).

Garnacho-Montero et al prospectively evaluated a group of critically ill patients with sepsis.¹³ Of 64 included patients, 54% developed electrophysiologic evidence of neuromuscular abnormalities. Electrophysiologic abnormalities alone, without clinical confirmation of weakness, were associated with longer duration of mechanical ventilation (34 d vs 14 d, $p < 0.001$), greater number of weaning days (15 d vs 2 d, $p < 0.001$), longer ICU and hospital length of stay, and higher hospital mortality (47.1% vs 20%, $p = 0.03$). Multivariate analysis revealed that neuromuscular disorders were the only independent risk factor associated with prolonged mechanical ventilation (odds ratio 15.4, 95% confidence interval 4.55–52.3, $p < 0.001$). Van den Berghe et al used multivariate analysis and found that the reduction in electrophysiologically diagnosed neuromuscular abnormalities that occurred with intensive insulin therapy was independently associated with a reduction in prolonged mechanical ventilation.⁹⁴ These 3 studies suggest that both ICU-acquired weakness and electrophysiologic abnormalities are important predictors of relevant patient outcomes.

Several prospective studies, including the one described above, have found that ICU-acquired neuromuscular disorders are associated with increased mortality. Leitjen et al studied a mixed population of critically ill, mechanically ventilated patients and reported an ICU mortality of 48% in patients with ICU-acquired neuromuscular abnormalities, versus 19% in patients without abnormalities ($p = 0.03$).²³ In patients with sepsis and electrophysiologically-defined neuromuscular abnormalities, in-hospital mortality was 84%, compared to 56.5% in patients without

abnormalities.⁴ Multivariate analysis found that neuromuscular abnormalities independently predicted in-hospital mortality in that study (odds ratio 7.1, 95% confidence interval 1.54–32.75). De Jonghe et al found that, among patients who survived long enough to awaken and undergo clinical examination, death in the ICU occurred in 4/26 (17%) of patients with weakness, compared to 4/71 (4%) of patients without weakness ($p = 0.20$).¹ Although that difference is not statistically significant, the trend suggests that weakness identified during early recovery from critical illness may be associated with a high risk of death, as is the presence of neuromuscular abnormalities by electrophysiologic testing early in the course of illness.

The rate of recovery of muscle strength among survivors with ICU-acquired neuromuscular disorders is highly variable, with some patients recovering fully in weeks and others remaining severely weak for years. Latronico et al recently summarized the results from 36 studies that reported long-term outcomes in 263 patients who were diagnosed with ICU-acquired neuromuscular disorders.¹⁰³ The mean duration of follow-up was 3–6 months, although some patients were followed for up to 8 years. Sixty-eight percent of the patients had complete functional recovery, whereas 28% had severe disability, with difficulty walking and/or breathing. The interpretation of these data is limited by the highly variable duration of follow-up. In addition, long-term follow-up in small studies is limited by the high ICU, post-ICU, and post-hospital mortality reported in patients with ICU-acquired neuromuscular disorders.^{56,104}

In their prospective study of ICU-acquired weakness, De Jonge et al found that nearly all evaluable patients (16/24) had recovered some strength by 9 months of follow-up, with two thirds living at home.¹ Zifko studied 13 patients with ICU-acquired weakness and electrophysiologic evidence of polyneuropathy 13–24 months after discharge (mean 17 mo).¹⁰⁰ All the patients had suffered from SIRS during their ICU stay. At follow-up, 2 patients had normal physical examinations, 1 patient had persistent severe weakness, four had mild weakness, and the remainder had sensory and/or focal motor abnormalities. All had electrophysiologic abnormalities. De Seze et al followed 19 patients who had been transferred from an ICU to a specialized neurologic rehabilitation unit for recovery from critical-illness polyneuropathy; all had diffuse weakness, and six had severe weakness (quadriplegia).¹⁰⁵ Complete recovery occurred in 4 patients (21%) at 3 months, 4 patients at 6 months, and 3 patients (16%) at 12 months. Two patients died between 6 months and 9 months with quadriplegia, and four had persistent quadriplegia at 2 years of follow-up. These latter 2 studies paint a relatively grim picture in terms of the long-term recovery from ICU-acquired neuromuscular disorders.

Several studies have found that survivors of critical illness have sustained impairments in physical function and

health status, even after one year of recovery.^{106–109} Muscle weakness appears to contribute substantially to disability after critical illness,^{107,110} and it is likely that ICU-acquired neuromuscular disorders play an important role in this weakness. Fletcher et al studied 22 patients who had been cared for in the ICU for ≥ 28 days.¹¹⁰ All patients had sepsis and at least 2-organ failure during their ICU stay; two had been diagnosed with critical-illness polyneuropathy, and one with necrotizing myopathy. Subjects were a year or more removed from ICU discharge (median 42.5 mo) at the time of follow-up, and yet all still complained of extreme weakness. Although only one third of the patients had weakness on physical examination, all but one had electrophysiologic evidence of critical-illness polyneuropathy. Of note is that 25 patients initially contacted for this study refused to participate; thus, the results reflect the findings from a highly motivated and perhaps more functional subgroup of patients, and may underestimate the true weakness-associated morbidity among survivors of critical illness. Nonetheless, this study provides persuasive evidence that ICU-acquired neuromuscular disorders are a major contributor to long-term disability after critical illness.

It is unclear whether the primary underlying pathology of ICU-acquired weakness (neuropathy vs myopathy) affects long-term recovery. In part, this differentiation is complicated by the aforementioned deficiencies in electrophysiologic testing and the lack of muscle biopsies in the majority of studies, in that many patients once thought to have critical-illness polyneuropathy probably had myopathy as the primary or a contributing cause of weakness. In one study of patients evaluated for neuromuscular weakness during their ICU stay, patients diagnosed with critical-illness myopathy (many confirmed by biopsy) had a similar course of recovery to those with critical-illness neuropathy, with the vast majority of patients ambulatory by 12 months in each group.⁴⁵ Of note, 3 patients with myopathy were not ambulatory at 12 months, which confirms that the course of this entity is not always benign.

Diagnosis

The clinical diagnosis of ICU-acquired neuromuscular disorders is suspected in the presence of unexplained weakness in patients recovering from critical illness; weakness can be so severe as to be confused with coma. Metabolic, pharmacologic, and central-nervous-system causes of weakness must be ruled out prior to establishing the diagnosis. Electrophysiologic testing is useful primarily to exclude other (possibly treatable) causes of severe weakness, including prolonged neuromuscular blockade and Guillain-Barré syndrome.^{5,7,101} As noted earlier, polyneuropathy can be difficult to distinguish from myopathy, unless direct muscle stimulation is used. Muscle biopsy can con-

firm or exclude myopathy as a cause of weakness, but is not recommended as a routine course, given its invasive nature and the lack of evidence that the information gained will influence prognosis or therapy.

As discussed earlier, routine screening of patients by electrophysiologic testing will identify more patients with neuromuscular abnormalities than will clinical examination, particularly if performed early in the course of illness. In a prospective evaluation of critically ill, mechanically ventilated patients, abnormal electrophysiologic test results at ICU days 4, 8, and 14 were associated with severe weakness in 0/5, 6/14 (43%), and 6/10 (60%) of patients, respectively (drop-out occurred due to death).⁷³ Milder degrees of weakness were not reported in this study, and it is unclear if electrophysiology correlates with clinical findings across a broad spectrum of disease. However, outside the context of research, it is not clear that early electrophysiologic testing provides sufficient information to justify the cost, given that there are no known therapies for ICU-acquired abnormalities at this point.

Prevention and Therapy

The only intervention thus far shown to reduce the incidence of ICU-acquired neuromuscular disorders is intensive insulin therapy.⁹ Maintenance of serum glucose at 80–110 mg/dL, compared to a conventional glucose goal of 180–200 mg/dL, reduced electrophysiologically diagnosed polyneuropathy by 49% in patients in the ICU for ≥ 7 days.^{9,94} Unfortunately, polyneuropathy was not a reported end point in a more recent study of intensive insulin therapy in medical ICU patients.¹¹¹

Experience from one small series of patients suggests that intravenous immunoglobulin may reduce the likelihood of developing critical-illness polyneuropathy.¹¹² Further study is needed prior to recommending this intervention, however.

It is likely that avoidance of potentially triggering or priming factors, such as corticosteroids and neuromuscular blocking drugs, will reduce the incidence of ICU-acquired neuromuscular abnormalities, as will avoidance of ICU-associated infections and prompt treatment of sepsis. If the previous statement is true, advances in ICU care will be associated with a reduction in ICU-acquired neuromuscular disorders.

There is no established treatment for patients with ICU-acquired weakness. Avoidance of drugs that may further perpetuate injury is obviously warranted. Physical therapy and rehabilitation may be helpful in accelerating recovery, but there is a lack of rigorous evidence to support this practice.¹¹³

Summary and the Future

Unfortunately, our understanding of the causes of ICU-acquired neuromuscular abnormalities remains limited by the lack of basic science and translational studies. There have been a few animal models that adequately reproduced the clinical conditions that predispose to ICU-acquired weakness, and although existing animal models do provide some insight into myopathic processes, the nature of the nerve injury remains unclear. Preventive and therapeutic strategies cannot be logically pursued without a better understanding of the basic science of ICU-acquired neuromuscular disorders. In addition, larger and more systematic long-term studies of patients with ICU-acquired weakness are needed to better guide rehabilitative strategies. Given the high incidence and potential costs of ICU-acquired neuromuscular disorders, the need for and the likely benefits of further research in this area are evident. In the interim, preventive strategies are limited to the provision of excellent ICU care in an effort to limit duration of stay and the subsequent development of secondary complications of critical illness, with the inclusion of intensive insulin therapy.

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Discussion

Rajiv Dhand: I have 2 comments. One is related to hyperglycemia. In the literature that you reviewed, did you find that diabetes was an independent risk factor for development of this problem? And the related comment was that we always think of corticosteroids as causing myopathy, but is it also possible that corticosteroids are having the effect through causing hyperglycemia?

Deem: I haven't come across anything that relates diabetes to critical illness polyneuropathy, although, given that diabetics have neuropathy, you might think it'd be a risk factor. It's mainly just hyperglycemia that shows up. I think only the studies by Van den Berghe et al^{1,2} have really addressed the independence of corticosteroids and hyperglycemia. They suggested that it was glycemic control and not other factors that related to the risk of developing polyneuropathy per se.

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Rajiv Dhand: And my second comment is that peripheral muscle weakness is obviously a problem, but I think the weakness that we are most concerned about is the phrenic-nerve diaphragm weakness. As you know, phrenic-nerve involvement and dia-

phragm weakness are really what have the most impact in the ICU.

Over the last couple of years I've become very conscious of the fact that you can find a lot of weakness in the diaphragm and involvement of the phrenic nerve without having much peripheral muscle weakness, or very gradually progressive peripheral-muscle weakness. In fact, we recently had a patient with obstructive sleep apnea, congestive heart failure—multiple comorbidities—and he was admitted because he had an olecranon bursitis. He would not take a noninvasive mask and so on. But to cut a long story short, we found that the reason that he had the olecranon bursitis was that he had to use his elbow to support his chin, and over the years, this problem had progressed very gradually. When we tested him, we found that he had profound respiratory-muscle weakness.

So there may be an expanded role for electrophysiological studies, because you may not find much weakness in the peripheral muscles, yet have significant weakness in the respiratory muscles. One of the reasons for distinguishing between polyneuropathy and myopathy would be to figure out whether this was primarily a problem related to the phrenic nerves, or was it a problem primarily related to the diaphragm itself?

In this respect, IVIG [intravenous immunoglobulin] may actually play a very important role, because about a couple of years ago we saw a patient who presented with one hemidiaphragm elevation, and, actually, Upinder [Dhand] played a very important role in the treatment of that patient. So, first of all, we thought that this was just a unilateral diaphragm in-

volvement, which should not be important, but the patient started becoming more and more symptomatic. There was objective evidence of loss of pulmonary function, and the diaphragm elevation went on getting higher. Phrenic-nerve testing showed that this was an idiopathic unilateral involvement of the phrenic nerve on that side. And because she was progressively getting worse, we gave her a trial of intravenous immunoglobulin for 5 days. Upinder did that. And, lo and behold, the patient improved symptomatically; she improved her pulmonary function, and actually the elevation of the diaphragm got better too. There is a possibility that by distinguishing whether this is a nerve involvement or a muscle involvement we may be able to better target our treatment for these patients.

Deem: I agree entirely. Few studies have looked at diaphragm and phrenic-nerve function in these syndromes, and they've only looked at a few patients. But it does appear to be a real entity. And electrophysiologic abnormalities are much more common than weakness per se, but that doesn't necessarily mean that there aren't actually functional abnormalities that are just too subtle for us to detect by examination. About the intravenous immunoglobulin: did that patient have evidence of demyelination?

Upinder Dhand: Actually, the electrophysiologic study was remarkable for demyelination changes. The distal latency of the phrenic nerve, instead of being 7 ms, was 22 ms, so it was markedly prolonged. It improved after treatment; it came down to 14 ms, with higher amplitude of motor po-

tential, so it improved both clinically and electrophysiologically.

Deem: Right. That illustrates how electrophysiologic testing might be useful in patients with ICU-acquired weakness syndromes.

Upinder Dhand: I want to point out that we should not mix up just the phrenic-nerve conduction abnormality with the ICU neuropathy. It could be important, because we're not sure if the critical illness neuropathy will benefit from intravenous immunoglobulin. There are a few reports, but we still don't know. Whereas this patient was possibly a variant of multifocal motor neuropathy. So she was completely different etiologically.

Deem: Wijdicks et al, from the Mayo Clinic, reported on a small group of patients with polyneuropathy who received intravenous immunoglobulin and it had no effect on their course.¹

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Benditt: I couldn't agree more. I think a lot of physiologic testing turns up some things that you might not have expected, so I agree with that. Concerning the recent increase in use of corticosteroids in the ICU,¹ and relative or absolute adrenal insufficiency, do you think it's overall a good thing or a bad thing that we're using steroids more commonly?

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Deem: I wish I knew the answer to that question. I think some Canadians are doing another trial of steroids for sepsis, or am I confusing that with an insulin?

Mehta: They are conducting a trial with the Australians to evaluate the effects of aggressive insulin therapy, with adult and pediatric patients, on adrenal function in the ICU.

Deem: OK, well, I think we really need more data, because I'm confused by the results of that study. I do give steroids to patients with septic shock, and then I stop them if they turn out to be responders. But that's not what they did in that study, and I don't know that what I'm doing actually results in better short-term patient outcomes, and they really didn't look at long-term outcomes in those patients. I think that's an important end point that we need to start including in our studies of interventions that we do in the ICU, because we may find out that in the long run we're actually harming more patients than we help.

Jubran: Steve, I think we have to be careful of generalizing too much from the data from the Van den Berghe et al study¹ about using insulin for polyneuropathy. The first study in which they found benefits from intensive insulin therapy was done in a surgical ICU. Also, they are more aggressive in providing nutrition to the patients than we routinely are in our ICUs. In fact, when the investigators repeated the study in medical ICU patients, they did not find a difference in mortality. I don't think they looked at critical-illness polyneuropathy in the second study, but hypoglycemia was an independent predictor of death.

REFERENCE

1. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354(5):449-461.

Deem: I agree that it's all so confusing—much like the literature on steroids for septic shock. On the other hand, I think we shouldn't look at their follow-up study as being a negative trial, because in some ways it was ac-

tually a positive trial. It did show lower morbidity and no difference in mortality, certainly, and there was a trend toward lower mortality in the intention-to-treat group. And in the patients who were there longer, there were even more benefits. I have no reason to believe that intensive insulin therapy won't reduce polyneuropathy in the medical ICU population. And in their study the reported incidence of electrophysiologically-diagnosed polyneuropathy was about 50% in the control group, which is in the range reported throughout the literature on this subject. So I don't think the way they treated patients with, for instance, total parenteral nutrition, was contributing to a higher risk of polyneuropathy. I take your point, that it is difficult to generalize the results from the first study, but I still think the evidence is convincing enough, at least for me, to continue with that approach in the general ICU population.

Rajiv Dhand: While we continue using intensive insulin therapy for our patients, I think I completely agree with Amal; I was quite disappointed by the most recent study, in which there was no difference in the primary outcome, and in the secondary outcomes.¹ All the differences were shown, but no Bonferroni correction was applied for those outcomes. So, really, this appears to be a totally negative study.

REFERENCE

1. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354(5):449-461.

Deem: Of course, we really aren't here to debate that study, but I think it depends on which data you look at, because the hazard ratios of various complications were reduced, and I don't think those have to be corrected in any fashion.

Rajiv Dhand: You're right about that.