Intensive care unit-acquired weakness

Richard D. Griffiths, BSc, MBBS, MD, FRCP, FHEA; Jesse B. Hall, MD, FCCP

LEARNING OBJECTIVES

After participating in this activity, the participant should be better able to:

1. Describe the incidence and etiology of intensive care unit-acquired weakness.
2. Explain the differential diagnosis and outcomes of intensive care unit-acquired weakness.
3. Use this information in a clinical setting.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: **Severe weakness is being recognized as a complication that impacts significantly on the pace and degree of recovery and return to former functional status of patients who survive the organ failures that mandate life-support therapies such as mechanical ventilation. Despite the apparent importance of this problem, much remains to be understood about its incidence, causes, prevention, and treatment.**

Design: **Review from literature and an expert round-table.**

Setting: **The Brussels Round Table Conference in 2009 convened more than 20 experts in the fields of intensive care, neurology, and muscle physiology to review current understandings of intensive care unit-acquired weakness and to improve clinical outcome.**

Main Results: **Formal electrophysiological evaluation of patients with intensive care unit-acquired weakness can identify peripheral neuropathies, myopathies, and combinations of these disorders, although the correlation of these findings to weakness measurable at the bedside is not always precise. For routine clinical purposes, bedside assessment of neuromuscular function can be performed but is often confounded by complicating factors such as sedative and analgesic administration. Risk factors for development of intensive care unit-acquired weakness include bed rest itself, sepsis, and corticosteroid exposure. A strong association exists between weakness and long-term ventilator dependence; weakness is a major determinant of patient outcomes after surviving acute respiratory failure and may be present for months, or indefinitely, in the convalescence phase of critical illness.**

Conclusion: **Although much has been learned about the physiology and cell and molecular biology of skeletal and diaphragm dysfunction under conditions of aging, exercise, disuse, and sepsis, the application of these understandings to the bedside requires more study in both bench models and patients. Although a trend toward greater immobilization and sedation of patients has characterized the past several decades of intensive care unit care, recent studies have demonstrated that early physical and occupational therapy, including during the period of intubation and ventilator support, can be safely performed and will likely improve patient outcomes with regard to functional status. (Crit Care Med 2010; 38:779–787)**

Key Words: ICU; weakness; muscle; myopathy; neuropathy; outcome; rehabilitation

Although patients are on occasion admitted to the intensive care unit (ICU) because of a neuromuscular disease that has or is at risk of producing respiratory failure, a much more common scenario is the development of weakness in the course of treatment of acute illness syndromes such as sepsis and/or respiratory failure. As a complication of critical illness, weakness frequently slows and even dominates the course of recovery from critical illness. The Brussels Round Table Conference in 2009 was dedicated to the topic of ICU-acquired weakness (ICU-AW) with the broad task of encompassing bench research to patient outcome and therefore was convened with a variety of clinicians, physician scientists, and basic investigators to explore our understanding of this phenomenon. This article spe-

Professor of Medicine (Intensive Care) (RDG), Pathophysiology Research Unit, School of Clinical Sciences, University of Liverpool, Liverpool, United Kingdom; Professor of Medicine, Anesthesia, and Critical Care (JBH), and Section Chief (JBH), Pulmonary and Critical Care, University of Chicago, Chicago, IL.

For information regarding this article, E-mail: rdg@liverpool.ac.uk

DOI: 10.1097/CCM.0b013e3181cc4b53

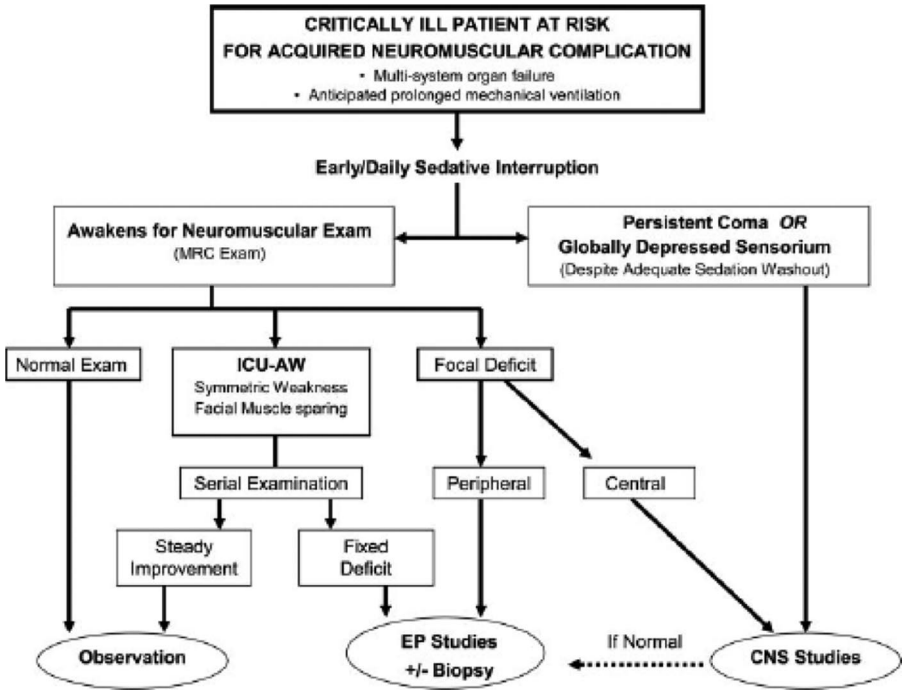

Figure 1. An algorithm for assessing neuromuscular complications in the critically ill. *EP*, electrophysiological.

cifically draws on, and is mostly limited to, the deliberations of these participants. Their individual contributions appear in a separate supplement of *Critical Care Medicine* 2009; 37(Suppl 10):S295–S461. An acknowledgment and full listing of the Round Table participants is located in the Appendix.

Definitions, Diagnostic Testing, and Nosology

Wasting syndromes have long been known to accompany protracted infection and diverse chronic illnesses, including malignancy and chronic obstructive pulmonary disease (1). Beginning in the 1980s, a descriptive literature arose describing both polyneuropathy and myopathy in some patients cared for in the ICU, often with underlying sepsis and/or respiratory failure, that appeared to be acquired during the course of their critical illness (2–7). The terms critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) were applied to the more clear-cut examples of each.

The primary means of distinguishing CIP and CIM involve electrophysiological testing and histologic evaluation of involved tissues (8). Use of nerve conduction studies and electrical myography are reasonably sensitive techniques to detect physiological abnormalities, and electrophysiological testing can even be extended to include nerve stimulation as a means of quantifying muscle force generation in a controlled fashion in patients in the ICU (9). In a recent prospective cohort study (10), 92 critically ill patients were followed for up to 1 yr after ICU admission with serial electrophysiological testing. Thirty percent of patients met criteria for CIM and CIP, and some had profound neuromuscular dysfunction persisting through the period of observation. Patients with CIP appeared to fare poorly compared with patients with isolated CIM.

There are limitations to an approach mandating electrophysiological screening of all patients outside of a research context (1). There are considerable costs associated with these tests, and hence they are often not available and certainly not available as routine longitudinally. Some patients have features of both CIM and CIP, and some patients without significant abnormalities have significant weakness, perhaps as a result of simple muscle atrophy. Differences in treatment between CIP and CIM are not clear-cut; hence, for the individual patient, identifying functional weakness and addressing it may be more important than attempting to partition its causes to either peripheral nerves, muscle, or both.

For these reasons, many advocate an approach of identifying ICU-AW more generally and without formal electrophysiological testing in the clinical setting. Such an approach is shown in Figure 1. Because bedside testing of the peripheral nervous system cannot occur apart from assessment and optimization of central nervous system function, coordinating examination of peripheral neuromuscular function with holidays from sedatives and other centrally acting agents is important. In many patients, independent central nervous system pathologies will need to be suspected, identified, diagnosed, and characterized pari passu with consideration of the general issue of weakness. Validated and simple-to-use assessment tools such as the Medical Research Council examination of muscle strength can be adapted for routine use in ICU populations to track ICU-AW.

Incidence and Outcomes

The reported incidence of ICU-AW depends greatly on the tools used to define it, as described previously, and the patient population studied (1). In one study of patients undergoing mechanical ventilation for >7 days, 25% were found to have clinically significant ICU-AW (11). In another investigation relying in part on electrophysiological abnormalities to define ICU-AW, patients ventilated for >7 days in the ICU exhibited an incidence of CIM and CIP of 58% (12). In studies of critically ill patients with sepsis, the incidence of ICU-AW is extremely high, reported to be present in 50% to 100% of patients (13, 14). Thus, apart from the clinical tools and definitions used to describe this general phenomenon, it appears to be an extremely common complication of critical illness.

As important as the frequency of weakness during ICU stay, there is the association with adverse longer-term outcomes. Several studies have shown that ICU-AW is associated with a longer duration of mechanical ventilation, which appears to reside in the phase of transition to liberation from the ventilator; this protracted ventilator dependence is also associated with increased duration of ICU and hospital stay (15, 16). Two other observational cohort studies have described an association between ICU-AW and mortality from critical illness (12, 17). Although attempts were made to use statistical methods to adjust for imbalances in clinical characteristics between weak and

nonweak cohorts, it is possible that weakness may simply be a marker for severity of illness as opposed to an independent cause of death in the critically ill.

Regardless of the impact of ICU-AW on acute outcomes from critical illness, there has been growing but incomplete awareness of the extent to which this consequence of critical illness impacts on the need for care after the ICU and the extent to which weakness impairs the pace and degree to which patients recovering from critical illness return to prior functional status. In a comprehensive evaluation of patients recovering from acute respiratory distress syndrome at 3, 6, and 12 months after critical care management, muscle wasting and weakness were the most prominent extrapulmonary conditions noted and were responsible for major functional limitations and disability (18). Limitations to recovery persisted in these patients over even longer periods of time as well (19). In a compilation of multiple studies following patients with ICU-AW and aggregating patients for analysis, 28% were noted to exhibit quadriparesis or paraparesis for extended periods, and even in patients with complete functional recovery, varying degrees of muscle atrophy and peripheral neuropathy were observed (10, 20, 21). The implications of these findings are clear; identifying methods to limit the extent of injury to the peripheral nervous system should be a part of our critical care management and following our patients long-term. Using the optimal methods of rehabilitation will be essential to enhance functional recovery after ICU management.

Risk Factors

With only more recent development and study of experimental animal models to investigate mechanisms of ICU-AW (22), much understanding of its evolution derives from observational studies that describe various risk factors associated with its development in patients.

Both retrospective and prospective trials have shown that severity of illness, as measured by standard severity of illness scores and the presence of a systemic inflammatory response syndrome are strongly associated with the development of ICU-AW (11, 23–26). Although it is appealing to consider that this association implies local inflammatory phenomena that result in nerve and muscle dysfunction, global markers of inflammation such as tumor necrosis factor-α and interleukin-6 levels have not been shown to be elevated in patients with ICU-AW compared with nonweak comparator populations (27).

A number of medications have been implicated as causes of ICU-AW with most attention focusing on neuromuscular blocking agents and corticosteroids. In animal models, corticosteroids can produce very significant muscle atrophy (28), and when these agents are combined with denervation, an injury similar to CIM is seen (1). This experimental observation may relate to the high incidence of myopathy seen in patients with status asthmaticus undergoing mechanical ventilation who are exposed to both corticosteroids and neuromuscular blocking agents (29). In patients enrolled in a trial to determine the effect of corticosteroids on proliferative-phase acute respiratory distress syndrome, an increased incidence of weakness and recurrent ventilator failure was observed in patients receiving corticosteroids compared with placebo (30).

Ideal glycemic control for critically ill patients remains a controversial topic with regard to appropriate patient selection and best targeted glucose level, but some trials have demonstrated that tighter control of blood sugars is associated with a reduction in the incidence of CIP (31). This benefit appears to derive from the glucose control itself as opposed to a direct action of insulin (32). Prevention of ICU-AW by specific algorithms to control blood sugars to any given range has not been demonstrated to date.

Immobility itself may be a significant risk factor for the development of weakness in the ICU. This notion is supported by many studies that demonstrate muscle atrophy during immobilization (see below) and the rapid development of diaphragm atrophy in organ donor patients undergoing controlled mechanical ventilation. However, some studies have shown that healthy volunteers do not develop significant reductions in muscle force or fatigability with immobilization, suggesting that immobility may be most detrimental when occurring in combination with other insults present during critical illness.

Pathophysiology

The pathophysiology of weakness developing within the ICU involves the interplay of factors arising from either the reduction in physical activity or the disease processes that have given rise to the admission. Our neuromuscular machine evolved to facilitate a regular high level of physical activity combined with the capacity to withstand intermittent nutritional insufficiency of protein. The result is a large and highly plastic skeletal muscle system that accounts for some 40% of body mass and 50% body protein, which responds closely to activity level, stress, and the changing functional demands of metabolism and inflammation. The maintenance of skeletal muscle, its metabolic interrelations, and importantly, early resumption of normal activity may be critical to survival (33) Skeletal muscle plays a central role in glucose homeostasis and contributes to >50% of whole-body glutamine supply (34).

The clinical symptoms and the pathologic changes seen in the critically ill patient occurring both early and later in the ICU stay are consistent with the highly regulated and complex control system integrating the function of the brain along peripheral nerves through muscle to the contractile machinery. It is not surprising that a deficit at any point in that chain of command can give rise to weakness and that these deficits may be multiple. It is now recognized that in patients, there is a pathologic continuum variable in extent and location that impairs many aspects of nerve and muscle function.

In the very severely ill patient, the catabolic breakdown of muscle proteins shows extreme losses approaching 2% per day (35) and a daily decrease in the fiber area of up to 3% to 4% (36). Muscle biopsies show the greatest atrophy in the contractile myosin filaments with relative preservation of other structural proteins. The normal myosin–actin ratio of 1.5 can decline acutely to 0.5 and can take several months to recover, and transcriptional regulation of myofibrillar protein synthesis plays an important role in this process (37). The septic ICU patient shows increased proteosome proteolytic activity (38). In sepsis models, multiple proteolytic and transcription pathways are active (39). There is also evidence of a vasculopathy with marked endothelial activation in both nerve (40) and muscle (41). This combination of inflammation and vascular pathology is common to many organ systems involved in multiple organ failure.

Unloading a Muscle

An important contributor to muscle weakness is the loss of mechanical loading resulting from physical inactivity, bed rest, or immobilization (42). Immobilization limits the shortening of affected muscle groups but allows development of isometric force, whereas in contrast, in bed rest (humans), spaceflight, lower limb suspension, and hind limb unloading (rodents), the resistance to shortening is largely abolished and changes in muscle length are not impeded. Care must be taken in the interpretation of the model used and in comparing small animals with humans in which differences have been noted.

Mechanical unloading stimulates a complex adaptive response that results in muscle atrophy and loss of specific force. A characteristic feature of an unloaded muscle is that it has the same number of thick filaments but fewer actin filaments; therefore, the force per cross-section is lower (43). It should be noted that this process is distinct from the more overt loss of myosin thick filaments seen in septic patients with multiple organ failure, confirming that unloading alone is but one mechanism. Unloading of muscle can cause both a slowing of protein synthesis (44) and an accelerated protein degradation (45–47). Evidence suggests these responses are promoted by concurrent development of oxidative stress caused by increased production of reactive oxygen species (48).

The Diaphragm

Unloading or inactivity of the diaphragm in the ICU is a major concern. Prolonged controlled mechanical ventilation (CMV) can promote diaphragmatic atrophy and contractile dysfunction (49); as few as 18 hrs of CMV can result in diaphragmatic atrophy in both laboratory animals and humans (50). Animal studies suggest that mechanical ventilation using a pressure support mode may limit ventilator-induced protein catabolism (51, 52), but measures of atrophy have not been made. Inactivity of the diaphragm is a major problem, but even short (i.e., 5-min) periods of intermittent spontaneous breathing during CMV may have the potential to retard the damaging effects of CMV on diaphragmatic contractile dysfunction (53).

In parallel to the short time course of CMV-induced atrophy, prolonged CMV promotes a time-dependent and progressive decrease in diaphragmatic-specific force production at both submaximal and maximal stimulation frequencies (54). Six hrs of CMV is associated with a 30% decrease in mixed protein synthesis and a 65% decline in the rate of myosin heavy chain protein synthesis (55). Prolonged CMV activates several proteases in the diaphragm, including calpain, caspase-3, and the ubiquitin proteasome system of proteolysis. With CMV lasting >6 hrs, increases in biomarkers of oxidative injury occur (i.e., protein carbonyls and lipid peroxidation), and key contractile proteins such as actin and myosin are oxidized in the diaphragm (56). A redox disturbance occurs because of increased reactive oxygen species production and a diminished antioxidant capacity in the diaphragm (57). Treatment of animals with an antioxidant can impede CMV-induced diaphragmatic atrophy and contractile dysfunction (58).

Inflammation

After noninjurious exercise stimulus, the cytokine pattern observed in plasma contrasts with that observed after an inflammatory stimulus from sepsis or severe infections. In sepsis, the proinflammatory cytokines, tumor necrosis factor-α and interleukin (IL)-1β, dominate the inflammatory cascade, whereas interleukin-6, a cytokine with both pro- and anti-inflammatory effects, consistently dominates the cascade in response to exercise stimuli (59). IL-6 serves to regulate blood glucose homeostasis through stimulation of glycogenolysis and glucose release from the liver, and the anti-inflammatory effects of IL-6 include inducing IL-10 and IL-1ra and inhibiting tumor necrosis factor-α. In patients with chronic obstructive pulmonary disease, their increasingly sedentary lifestyle may be a primary contributor to profound limb muscle atrophy, but given that systemic chronic inflammation occurs in chronic obstructive pulmonary disease, this process may interact with inactivity to cause deleterious effect on skeletal muscle (60).

The inflammatory process in healthy people after exercise-associated muscle damage is dominated initially by a destructive phase that is tightly titrated and modulates a reparative, regenerative phase. Elevated levels of cytokines expressed locally within the muscle and detected in the plasma with increased expression of adhesion molecules on circulating leukocytes and on the muscle vasculature are early signs. A subsequent leukocyte invasion is central to the removal of damaged tissue and its successful regeneration. This later process is perhaps impaired in the critically ill because widespread leukocyte invasion into skeletal muscle is an uncommon histologic observation in patients in the ICU. Anti-inflammatory interventions aimed toward tempering muscle wasting and weakness in chronic obstructive pulmonary disease may not be beneficial because of longer-term disruption of the regeneration of muscle tissue (61). Exercise training for 8 to 10 wks that improved exercise capacity did not also lower plasma and muscle inflammatory cytokines or markers of muscle regeneration (62, 63). Whether chronic obstructive pulmonary disease-associated inflammation is directly linked to muscle wasting is complicated by the fact that patients with chronic obstructive pulmonary disease have extremely limited activity levels, which might be the primary cause of atrophy. In contrast to limb muscles, the respiratory muscles that are overused demonstrate beneficial training-like effects (64), and inflammation is not a common feature of abnormal morphology in the diaphragm in chronic obstructive pulmonary disease (65).

Sepsis

In sepsis, derangements occur at multiple subcellular sites involved in the pathway of excitation–contraction coupling, including decreased membrane excitability, injured sarcolemmal membranes, altered calcium homeostasis, and disrupted contractile protein interactions (66). Just as clinical sepsis covers a wide spectrum, the various animal research models used to study sepsis also can range from multiple organism septicemias down to endotoxemias, and this makes the interpretation of data a challenge. Sepsis induces a myopathy characterized by reductions in muscle force-generating capacity, atrophy (loss of muscle mass), and altered bioenergetics. Respiratory muscle strength declines within hours of induction of sepsis. Decrements in diaphragm-specific force generation (force normalized per muscle cross-sectional area) occur before any evidence of reductions in diaphragm mass or diaphragm protein content (67). Force generation and fatigability in the adduc-

tor pollicis muscle of critically ill septic patients were assessed and compared with data from normal individuals (before and after cast immobilization) (9). Although 2 wks of lower arm immobilization had no effects on force generation in control subjects, the force generation was severely reduced in the septic patients. In more prolonged models of sepsis, muscle wasting is a prominent feature and is thought to result from increased proteolysis and decreased protein synthesis (68), and reductions in both limb muscle force generation and mass occur (69).

Muscle in some circumstances appears to be electrically inexcitable (70) leading to the concept that ICU-associated weakness in some patients represents an acquired channelopathy involving dysregulation of sodium channels. It has been shown that a nonexcitable muscle membrane on direct muscle stimulation in ICU patients predicts ICU-AW (71). Membrane inexcitability also occurs acutely in the nerve in animal models and may explain the acute nerve dysfunction and its more rapid recovery seen in the critically ill (72). A chronic sepsis model showed evidence of decreased muscle membrane excitability, corroborating findings in the denervation steroid model (73). Diaphragm myofibers in septic animal models, visualized with a fluorescent tracer dye that did not enter cells with intact membranes, demonstrated a markedly greater level of sarcolemmal damage than in control animals. Mechanical ventilation in septic animals prevented sarcolemmal damage in the diaphragm (74).

Sepsis induces contractile dysfunction at the level of the myofilaments, and free radicals modulate these alterations (75, 76). Reductions in single-fiber force generation correlate closely with the observed reductions in muscle-specific force generation in intact muscles (e.g., single-fiber force generation and intact muscle force generation are reduced to the same degree) and therefore can explain much of the contractile dysfunction in sepsis. A superoxide scavenger (i.e., PEG-SOD) or an inhibitor of nitric oxide synthesis (N^G-nitro-L-arginine methyl ester) can attenuate endotoxin-induced reductions in muscle contractile protein force generation, providing evidence that free radicals are linked to sepsis-induced contractile protein dysfunction (77). A free radical scavenger (PEG-SOD) or a nitric oxide synthase inhibitor (L-NAME) can prevent both endotoxin-mediated physiological alterations in state 3 respiration and depletion and modification of selective mitochondrial proteins, implicating peroxynitrite (the reaction product of superoxide and nitric oxide) in the pathogenesis of sepsis-induced diaphragm mitochondrial dysfunction (78).

Muscle wasting occurs later in the course of systemic inflammation and results from increased proteolytic degradation as well as decreased protein synthesis (79). The mechanisms leading to sepsis-induced changes in skeletal muscle are linked to excessive localized elaboration of proinflammatory cytokines, marked increases in free radical generation (80), and activation of proteolytic pathways that are upstream of the proteasome, including caspase (67) and calpain (81). The ubiquitin ligases atrogin-1 and MuRF1 are marked features of muscle atrophy in sepsis (82, 83) and appear upregulated by the FoxO family (Forkhead box O) transcription factors in many different situations. Expression of constitutively active FoxO3 induces expression of multiple atrogenes, including atrogin-1, and causes atrophy of muscle. FoxO3 stimulates overall protein degradation coordinating proteosomal, but also lysosomal, proteolysis by activating autophagy (84). Glucocorticoid excess induces or exacerbates muscle wasting and is associated with expression and activity of these transcription factors, including FoxO 1, 3, and 4 as well as the nuclear cofactor p300 (28). Activation of the calpain system leads to the disruption of the sarcomere and release of myofilaments so that they can be ubiquinated and degraded by the 26S proteasome (85). Calpain activation (86) also inhibits Akt activity resulting in activation of FoxO transcription factors and GSK-3β and stimulation of muscle proteolysis with inactivation of mammalian target of rapamycin, therefore inhibiting protein synthesis. Inhibition of these pathways may alter the evolution and progression of sepsis-induced myopathy and potentially reduce the incidence of sepsis-mediated acquired weakness syndromes.

Protein Synthesis

In the critically ill, muscle loss is a result of an inability to maintain rates of protein synthesis above those of protein breakdown. Even when muscle proteolysis is stimulated massively, with a resultant rise in intracellular amino acids, the pool of available amino acids is not sufficient to stimulate and sustain muscle protein synthesis equal to breakdown, and net loss occurs.

The basal rates of muscle protein turnover in healthy older persons are not altered from those in younger adults (87). Rather, the ability to capture amino acids from the blood after feeding is compromised, and the response to increasing the amount of amino acids in the blood is limited and cannot fully overcome this anabolic resistance. Although insulin plays almost no role in stimulating muscle protein synthesis in human muscle, it is of great importance in inhibiting muscle protein breakdown (88). A 50% fall in muscle proteolysis occurs with only 15 $\mu U/mL^{-1}$ insulin in the presence of normal amino acid concentrations in young adults, whereas in older subjects, insulin has little effect. In studies in humans of either limb immobilization or extended bed rest, a reduction in muscle protein synthesis was sufficiently large to explain the observed fall in muscle mass without invoking any rise in muscle protein breakdown (89, 90) days. In contrast with small animal studies, these studies do not show any rise in proteolytic markers. Immobilizing patients in bed is likely to make it harder for them to maintain body protein, because they appear unable to respond to the normal feed stimulus of amino acids (91). Stress and inflammation elevate protein breakdown (92), and if this results in amino acids stimulating muscle protein maximally, one would predict that providing additional amino acids in nutritional form is unlikely to reverse muscle wasting while the patient remains inactive. Nutritive blood flow (93) is an important feature of the anabolic response to food and insulin and depends on the opening of a network of vessels in muscle, which is particularly sensitive to insulin at low concentrations. This is likely to decrease with age and immobilization, and a major problem may be shunting of blood flow past the metabolically active compartment, except for egress of amino acids (94).

Bed Rest

Traditionally, it has been considered that a "period in bed for the treatment of illness" or bed rest, is beneficial. Although short periods of rest and 6 to 9 hrs of sleep are necessary for repair and recuperation, and although reduced activity lowers metabolic demands, reduces hemorrhage, and may alleviate pain, there is little evidence that prolonged bed

rest (more than 24–48 hrs) has any benefit (95). Clinical studies invariably show more harm than benefit from enforced prolonged bed rest. Exercise has pronounced effects on immune signaling and, after a marathon run, IL-6 concentrations increased by approximately 100 times their levels at rest (96). IL-6 in the systemic circulation after exercise does not represent inflammation in damaged muscle. It has been shown that nondamaging exercise is a major stimulus to IL-6 release (97). In contrast to the effects of sepsis, concentrations of IL-1 and tumor necrosis factor-α do not increase substantially with exercise nor does IL-6 stimulate release of nitric oxide or matrix metalloproteinases. Rather, IL-6 is a strong inhibitor of the inflammatory cytokines tumor necrosis factor-α and IL-1, and it blocks IL-1 receptors and results in elevated concentrations in plasma of the anti-inflammatory mediators IL-1ra and IL-10. Regular exercise acting through IL-6 may reduce systemic vascular inflammation with decreased C-reactive protein (98), prevent atherogenesis, and improve insulin sensitivity. Given that tumor necrosis factor-α may trigger IL-6 release, it is possible that adipose-derived tumor necrosis factor-α is the "bad" driver of inflammatory processes, whereas skeletal muscle IL-6 might be a "defense" mechanism against the proinflammatory actions of tumor necrosis factor (99). Exercise may maintain this important IL-6 regulation of health and disease.

Within 48 hrs of recumbency, many critically ill patients show partial or complete atelectasis of the left lower lobe on chest radiographs (100). In healthy subjects, bed rest of just 5 days results in insulin resistance, higher blood glucose, and significant increases in blood concentrations of total cholesterol and triglycerides (101). Dysfunction of the systemic microvascular endothelium function may occur with inactivity and contribute to insulin resistance and nutritive supply to muscle. A reactive hyperemic response to 5 mins of large artery occlusion was significantly blunted after 5 days of bed rest (after only 3 days in the forearm) in normal subjects. The significance of these findings to critically ill patients is not known but may also increase the risk of multiple organ dysfunction, gastrointestinal bleeding, intestinal ischemia, and skin ulcers. Reducing the consequences of bed rest on muscle and joints has been shown through resistance exercise in normal subjects (102), continuous passive motion devices in the critically ill (103), and through electrical stimulation in patients with chronic obstructive pulmonary disease (104). Although activation of only part of the muscular system may show benefits, it is more likely that early ambulation or other forms of whole-body exercise will truly reverse the adverse consequences of bed rest.

Prevention and Treatment

Given the association ICU-AW with a number of risk factors, reducing patient exposure when possible to these risk factors would appear a prudent approach to patient care, even if the amount of data from prospective trials in large populations is scant or nonexistent for most of these risk factors. Accordingly, limiting critically ill patients' exposure to corticosteroids and neuromuscular blocking agents is a generally recommended approach to limit adverse affects on the peripheral nervous system (1, 29). Similarly, most authors believe some degree of glycemic control is needed for critically ill patients, but the target range to avoid undesirable hypoglycemia and its consequences remains a topic of active investigation. Whether early nutrition or the use of specific nutritional supplements or components will limit loss of muscle mass or enhance recovery from muscle loss remains an area of debate and exploration. Limiting patient exposure to excessive sedation and analgesia during mechanical ventilator support is another approach that can limit the duration of time on the ventilator, the duration of bed rest, and conceivably, the development of ICU-AW (105–107).

Most promising for the management of ICU-AW has been the demonstration in a number of recent studies of the feasibility and benefits of early, targeted physiotherapy for critically ill patients, even while they are undergoing life- and organ-support interventions. A number of studies have proven that mobilization of critically ill patients is safe (108, 109) and can be facilitated with modest additions of staff and equipment to the ICU (110). In a recent randomized controlled trial, investigators reported that early physical and occupational therapy, coupled with a sedative holiday, resulted in a reduction in the duration of mechanical ventilation, reduction in ICU length of stay, and reduction in the magnitude of delirium (111). In addition, there was a near doubling of the fraction of patients who had achieved independent functional status at the time of hospital discharge. Using a bedside cycle ergometer, another recent randomized controlled trial showed that in addition to standard physiotherapy, those who had passive (initially when sedated) and then moving to active cycling exercises in the ICU for 20 mins 5 days a week had an improved 6-min walking distance and physical satisfaction score at hospital discharge (112). If these benefits can be demonstrated to be durable over time and the results of these seminal trials confirmed in larger multicenter trials, this approach to early mobilization of patients, termed "animation" by the one of the authors, may become a standard approach to patient management.

CONCLUSIONS

ICU-AW is a common complication of critical illness, particularly in patients undergoing mechanical ventilation and/or with conditions leading to systemic inflammatory response syndrome. The weakness and disability that result from these neuromuscular disorders can dominate the long-term course and impede recovery. A number of risk factors associated with development of weakness during critical illness have been identified. Much remains to be understood regarding the pathophysiological pathways resulting in weakness, and lessons may be derived from studies of models of disuse, aging, chronic lung disease, and sepsis. Early trials have proven the feasibility of more aggressive use of physiotherapy early in the course of critical illness, and one prospective randomized trial has demonstrated enhanced recovery of independent functional status by such measures.

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APPENDIX: ROUNDTABLE MEMBERS

We thank and acknowledge the expert deliberations of the round table participants listed subsequently. Because of space limitations, the authors of this summary review of the roundtable do not attempt to be inclusive and take responsibility for any errors or omissions.

Organizer: Jean-Louis Vincent, Brussels, Belgium. Co-chairs: Richard D. Griffiths, Liverpool, UK; Jesse B. Hall, Chicago, IL. Participants: Elie Azoulay, Paris, France; Polly Bailey, Salt Lake City, UT; Laurent Brochard, Creteil, France; Roy Brower, Baltimore, MD; Leigh Callahan, Lexington, KY; Bernard De Jonghe, Poissy, France; Matthias Eickermann, Boston, MA; Greet Hermans, Leuven, Belgium; Margaret Herridge, Toronto, Canada; Malcolm Jackson, Liverpool, UK; John Kress, Chicago, IL; Nicola Latronico, Brescia, Italy; Dale Needham, Baltimore, MD; Scott Powers, Gainesville, FL; Michael Reid, Lexington, KY; Darlene Reid, Vancouver, Canada; Michael Rennie, Derby, UK; Tarek Sharshar, Garches, France; Robert Stevens, Baltimore, MD; Paul Wischmeyer, Denver, CO.