ABSTRACT

- **Objective:** To provide an overview of intensive care unit–acquired weakness (ICUAW), summarize recent clinical trials on early rehabilitation in the ICU, and highlight novel strategies that may minimize the burden of this syndrome.
- **Methods:** Review of the literature.
- **Results:** Over the past decade, studies have revealed that a significant proportion of survivors of critical illness suffer from profound neuromuscular weakness and consequent impairment in functional status and quality of life. Immobility, deep sedation, and inflammation likely contribute to the development of ICUAW. Clinical trials suggest that early rehabilitation during acute critical illness may minimize ICUAW and improve patient-important outcomes. Therapeutic strategies must incorporate a paradigm shift where multidisciplinary efforts at early mobilization are prioritized and supported. Novel technology and interventions, such as neuromuscular electrical stimulation and cycle ergometry, may facilitate early rehabilitation in critically ill patients.
- **Conclusion:** Future efforts are needed to identify barriers to the provision of early rehabilitation and to rigorously evaluate novel interventions.

**ETIOLOGY OF ICU-ACQUIRED WEAKNESS**

**Immobility and Disuse Atrophy**

Although bed rest has been thought to be necessary for recovery, prolonged immobility beyond 24 to 48 hours is associated with many detrimental physiological consequences (Figure) [1,2]. Bed-bound patients sustain muscle atrophy from the loss of mechanical loading required to maintain muscle length [3]. These unloaded muscles have fewer actin filaments resulting in a lower force per cross sectional area, which manifests clinically as muscle weakness. Unloaded muscles also have decreased protein synthesis and accelerated protein degradation [4]. Muscle atrophy may occur within hours of immobility in healthy subjects [5], leading to up to 5% loss of muscle strength for each week of bed rest [6]. Immobility increases production of pro-inflammatory cytokines and reactive oxygen species, resulting in further muscle proteolysis, with a net loss of muscle protein and subsequent muscle weakness [7].

The interaction of critical illness with immobility can further accelerate muscle loss [3]. Catabolic protein loss can be up to 2% per day in critically ill patients [4]. The muscle fibre area decreases by 4% per day with severe atrophy in contractile myosin filaments [8]. Increased severity of illness has also been associated with ICUAW [9–11]. The systemic inflammatory response syndrome (SIRS) in the context of inactivity has a more profound impact on muscle loss than with immobilization alone [10]. Inactive septic patients have decreased muscle protein synthesis, increased urinary nitrogen excretion (suggesting increased muscle catabolism) and decreased lower extremity muscle mass [12].

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Critical Illness Polyneuropathy and Myopathy

Bolton and colleagues first described critical illness polyneuropathy (CIP) in a case series of 5 patients with flaccid and areflexic limbs, unable to wean from mechanical ventilation [11]. Electrophysiological testing demonstrated severely reduced motor and sensory nerve action potential amplitudes. The nerve histopathology of affected individuals showed moderate to severe primary axonal polyneuropathy with mixed motor and sensory involvement and distal predominance. Latronico and colleagues subsequently described a case series of 24 ventilator-dependant patients with critical illness myopathy (CIM) in addition to axonal degeneration in nerve-affected patients [13]. Examination of the histopathology of the peroneus brevis muscle revealed that 58% of patients had evidence of primary myopathy, 21% had polynuromyopathy, and 92% had muscle atrophy.

Proposed Nomenclature

A framework for diagnosing and classifying ICUAW has been proposed, in which ICUAW represents clinically detectable weakness in which there is no plausible etiology other than critical illness [14]. Patients with ICUAW and documented polyneuropathy and/or myopathy can be further classified into 3 groups: (1) CIP, characterized by ICUAW with a mixed sensory-motor axonopathy; (2) CIM, characterized by ICUAW with metabolic, inflammatory, and bioenergetic muscle derangements and/or functional inactivation (ie, membrane inexcitability); or (3) critical illness neuromyopathy (CINM), characterized by ICUAW with combined muscle and nerve involvement. Broad consensus by clinicians and researchers on a common definition and diagnostic criteria for ICUAW would help to ensure consistent case identification and allow for more meaningful comparisons across studies and patient populations [15].
RISK FACTORS

Many risk factors have been implicated in the development of ICUAW, including prolonged immobility, systemic inflammation, and oversedation, but recent attention has focused on a number of controversial risk factors including corticosteroids, neuromuscular blocking agents, and hyperglycemia [16].

There has been conflicting evidence with respect to corticosteroids and neuromuscular blocking agents and the development of ICUAW. Corticosteroid use has been associated with significant muscle atrophy in animal studies [17]. While a number of observational studies have not confirmed a significant association between corticosteroids and ICUAW [18–21], post hoc analysis of a randomized control trial (RCT) evaluating use of methylprednisolone in acute respiratory distress syndrome (ARDS) showed all patients with ICUAW occurred in the corticosteroid group [22]. In patients mechanically ventilated for at least 7 days, the use of corticosteroids significantly increased the risk of developing ICUAW (odds ratio 14.9; 95% confidence interval 3.20–69.80), but there was no association with dose or duration of corticosteroid use [23]. The use of neuromuscular blocking agents was an independent risk factor for ICUAW in one observational study [21] but significant association with ICUAW were lacking in other large prospective studies [20,24,25]. In a recent clinical trial that randomized patients with severe ARDS to cisatracurium (a neuromuscular blocking agent) for 48 hours versus placebo, the incidence of ICUAW at ICU discharge was not significantly different between groups [26]. However, muscle strength testing in this study may not have been standardized and no functional assessment of neuromuscular function was made at ICU discharge or beyond. Furthermore, the composite Medical Research Council (MRC) score reported in this study represents a global measure of overall muscle strength and may be insensitive to the detection of weakness in individual muscle groups.

Finally, hyperglycemia may be an important risk factor for ICUAW. Post hoc analysis of 2 large RCTs of intensive insulin therapy had reported significant reductions in ICUAW with tight glycemic control [19,27]. However, these secondary analyses are hypothesis-generating, and given the potential risks of tight glycemic control [28], clinicians should be cautious in the use of this therapy solely for the prevention of ICUAW.

DIAGNOSIS OF ICU-ACQUIRED WEAKNESS

The diagnosis of ICUAW remains challenging. Many critically ill patients are exposed to prolonged immobility, sys-
ICU-ACQUIRED WEAKNESS

temic inflammation, and oversedation while in the ICU, putting a large number of patients at risk for ICUAW. However, routine screening of all ICU patients with electrophysiological testing (i.e., nerve conduction studies and or electromyography) is not feasible due to problems with cost and availability of both equipment and expertise, as well as challenges in testing (e.g., due to limb edema) and interpretation of the results in critically ill patients. Electromyography can detect abnormal muscle activity in the forms of fibrillation potentials and positive sharp waves. These EMG findings, however, suggest either a neuropathy or myopathy. A patient’s cooperation is required to evaluate the minimal or maximal voluntary contraction during an EMG test to distinguish neuropathic from myopathic processes. Given the lack of efficacious treatments for CIP and/or CIM, routine screening of patients at risk for ICUAW would not be warranted at this time.

We advocate that the starting point for the diagnosis of ICUAW should be bedside physical examination of peripheral muscle groups using the MRC sum score [29,30]. A composite MRC score from the examination of 3 muscle groups in each limb (range: 0 [no muscle contraction] to 5 [normal strength]) is commonly used [31], with < 80% of the maximum score (i.e., < 48 out of 60) representing ICUAW. This composite MRC score has excellent interrater reliability within certain ICU patients, as well as in survivors of critical illness [32].

EPIDEMIOLOGY

ICUAW is common, although the reported incidence varies depending on the case definition used and the population studied. In a systematic review of 24 studies using both clinical and electrophysiological testing, 46% of critically ill patients had neuromuscular complications, which were associated with increased duration of mechanical ventilation and ICU and hospital stay [33]. In a prospective cohort of 95 patients mechanically ventilated for at least 7 days, ICUAW was diagnosed clinically in 25% of patients [23]. In another prospective study utilizing electrophysiological testing, the incidence of ICUAW was 58% for patients ventilated for at least 7 days [24]. Among patients with sepsis, the incidence of ICUAW has been reported to be as high as 50% to 100% [34,35].

THE BURDEN OF ICU-ACQUIRED WEAKNESS IN THE CRITICALLY ILL

Persistent impairments in physical function and health-related quality of life are common in patients recovering from critical illness. Herridge and colleagues prospectively studied 109 ARDS survivors and found persistent functional disability up to 5 years after discharge from the ICU [36,37]. On average, patients had severe muscle atrophy and lost 18% of their baseline body weight in the ICU. Patients stated that their physical functional impairment was due to loss of muscle bulk, proximal muscle weakness, and fatigue. Entrapment neuropathies, foot drop, joint immobility, persistent pain at chest tube insertion sites and dyspnea were also described by patients [38]. At 1 year, over half of the patients could not return to work because they still experienced persistent fatigue and weakness and poor functional status. Beyond the physical disability is growing awareness that ICU survivors are also burdened by non-physical morbidity including depression, anxiety, post-traumatic stress disorder, delirium, and cognitive impairment [39,40]. The global impact of severe critical illness may result in debilitating disability that results in ongoing requirements for medical care, financial strain, and caregiver burnout (Figure) [41].

EARLY REHABILITATION IN THE CRITICALLY ILL

An important therapeutic option that has been evaluated over the last decade for prevention and treatment of ICUAW is early rehabilitation and mobilization of patients in the ICU [1]. Having critically ill patients participating in progressive rehabilitation (e.g., passive range of motion, active range of motion/bed exercises, sitting at edge of bed, transfers) leading to mobilization, despite the use of life support therapies, may reduce muscle atrophy and lead to improved strength and physical function. Moreover, mobilization and exercise may decrease oxidative stress and inflammation [1,7] and prevent insulin resistance and microvascular dysfunction [42], which may lead to a reduction in ICUAW.

There is accumulating evidence that early and accelerated rehabilitation improves both short- and long-term morbidity in specific groups of hospitalized patients, such as those with community-acquired pneumonia [43], mild traumatic brain injury [44], stroke [45,46], myocardial infarction [47,48], deep vein thrombosis [49], and infectious hepatitis [50]. In chronically critically ill patients admitted to a respiratory ICU (RICU), there is a single report of a RCT evaluating an early rehabilitation program [51]. Patients with COPD following an episode of acute respiratory failure (with approximately 50% requiring invasive mechanical ventilation) were randomized to intensive pulmonary rehabilitation (60 patients) versus
standard therapy (20 patients) after admission to a RICU. The pulmonary rehabilitation group started therapy within 24 hours of RICU admission and consisted of twice daily, 30- to 45-minute sessions focused on lower extremity and respiratory muscle training, with a goal of progressing to ambulation. The standard therapy group had no specific lower extremity or respiratory muscle training early in their RICU admission. While there was no significant difference between groups in proportion regaining the ability to ambulate (87 vs. 70%, P = 0.09), the pulmonary rehabilitation group had significantly greater improvements in 6-minute walk distance, maximal inspiratory pressure, and dyspnea scores from their baseline status, as compared to the standard therapy group.

Recently, observational studies have demonstrated that early mobilization, including ambulation, of mechanically ventilated patients is safe and feasible even when occurring shortly after physiological stabilization, within 24 to 72 hours of acute ICU admission [52–56]. In a cohort of 103 mechanically ventilated patients, rehabilitation was started within the first 24 hours of admission to a RICU, employing 2 daily sessions of physiotherapy lasting at least 30 minutes [54]. The majority (69%) of participants were able to ambulate over 100 feet prior to ICU discharge and adverse events were rare (<1% of all activities). In a similar cohort of 104 mechanically ventilated patients undergoing early rehabilitation, 88% were able to walk over 200 feet prior to ICU discharge [57].

A single-center, non-RCT in 330 mechanically ventilated patients demonstrated that a dedicated multidisciplinary mobility team (ICU nurse, nursing assistant, physical therapist), using a physical rehabilitation protocol, was associated with increased access to physical therapy and a shorter time for patients to be first out of bed (5.0 vs. 11.3 days, P < 0.001, adjusted for body mass index, severity of illness, and vasopressor use) [52]. Moreover, survivors that had been treated with the early mobility protocol experienced a decrease in ICU (5.5 vs. 6.9 days, adjusted P = 0.025) and hospital (11.2 vs. 14.5 days, adjusted P = 0.006) stay. In addition, there was a trend towards a reduction in both the duration of mechanical ventilation (8.8 vs. 10.2 days, adjusted P = 0.163) and hospital mortality (12% vs. 18%, P = 0.125), without a significant increase in hospital costs despite the added expense of the mobility team (mean cost per patient: $41,142 vs. $44,302, P = 0.262). Early mobility was also associated with a lower rate of hospital readmission in the first year after ICU discharge [58]. Finally, temporal trends indicating improved ICU and hospital length of stay and declining rates of tracheostomy (29% vs. 5%) and failure to wean from mechanical ventilation (12% vs. 3%) have also been reported [56].

Combining protocols for early mobility and sedation management may have synergistic benefits. Indeed, a recent RCT evaluating the use of early rehabilitation in the ICU randomized 104 mechanically ventilated patients to either early exercise and mobilization combined with daily interruption of sedation versus daily interruption of sedation alone [59]. Patients in the therapy group had physical and occupational therapy initiated early as compared to controls (median 1.5 vs. 7.4 days after intubation, P < 0.001), with few serious adverse events. Importantly, patients in the intervention group had shorter duration of delirium (median 2 vs. 4 days, P = 0.02) and more ventilator-free days (23.5 vs. 21.1 days, P = 0.05). Finally, a significantly greater proportion of patients returned to independent functional status at hospital discharge in the therapy group (59 vs. 35%, P = 0.02). These encouraging results require further investigation in multicenter randomized trials.

**CHALLENGES TO EARLY REHABILITATION**

Acute rehabilitation is not uniformly delivered across ICUs [60,61]. A number of important patient, health care provider, and institutional barriers to early rehabilitation, both real and perceived, represent significant challenges to translating this intervention into practice in many ICUs [62–65]. Consistently reported patient barriers to mobility have included medical instability, excessive sedation, and lines [64]. A recent Canadian survey of physicians and physiotherapists on acute rehabilitation in the ICU showed that insufficient health care provider knowledge, skills set, safety concerns, and delays in recognition of suitable patients were important barriers. [64] Institutionally, inadequate equipment and staffing has consistently been noted in national surveys [66]. The lack of protocols and few consensus guidelines on early mobilization also contributes to delayed rehabilitative efforts [53,67]. In a national survey of American hospitals, only 10% of all ICUs had established initiation criteria for activity and less than 1% of all ICUs had automatic physiotherapy requests [61].

An important step in developing a successful early rehabilitation program in the ICU requires a cultural paradigm shift away from bed rest and heavy sedation.
toward prioritizing awake, spontaneously breathing patients and a focus on early rehabilitation [68]. Creating a supportive ICU culture for early mobilization through interdisciplinary cooperation, coordination, and communication are integral to the successful and sustained implementation of this complex intervention [55,56,65]. Local representation and champions from each relevant discipline (eg, critical care, psychiatry, nursing, physical/occupational therapy, respiratory therapy) to create a vision and guiding coalition to prioritize early rehabilitation is key to transforming ICU culture [56].

The recognition of local barriers through a review of existing practices and discussion with health care providers from the disciplines of nursing, physical therapy, respiratory medicine, occupational therapy, critical care physicians, neurologists and rehabilitation experts can led to the educational initiatives to promote early rehabilitation [53,67]. With the growing number of critically ill patients in the context of already financially strained hospitals, clinicians will have a responsibility to advocate for resources and develop more efficient ways to sustain rehabilitation efforts. Hospital administrators may perceive the intervention of early rehabilitation in the ICU to be costly. However, the potential for decreased ICU and hospital length of stay from early rehabilitation programs may lead to enhanced resource utilization and improved patient satisfaction, resulting in a net cost savings on a larger scale [55,69].

**FUTURE DIRECTIONS**

Novel rehabilitation technology, such as neuromuscular electrical stimulation (NMES) and bedside cycle ergometry, may be useful adjunctive interventions to facilitate very early rehabilitation in critically ill patients [70]. NMES induces passive contraction of muscles through electrical impulses delivered through skin electrodes placed over target muscle groups (eg, quadriceps) and may help in ameliorating the development of muscle atrophy and weakness among high-risk critically ill patients during the acute phase of their illness when they may remain heavily sedated [71,72]. Bedside cycle ergometry can provide muscle strength training and range of motion exercises for ICU patients who are either awake (active cycling) or sedated (passive cycling), and may also preserve muscle strength and function [73]. The potential role of these rehabilitation interventions in critically ill patients require further study in large, prospective clinical trials.

Oversedation, delirium, and enforced bed rest are common barriers to early rehabilitation in the ICU. The use of sedation and analgesia (with or without neuromuscular blockade) in the ICU is ubiquitous for management of patient discomfort, anxiety, and patient-ventilator asynchrony. A change in the approach to the sedative use in the ICU, including use of dexmedetomidine [74], intermittent/symptom-targeted sedation [75], or no sedation [76], may help to limit oversedation and delirium in the ICU and improve patient wakefulness and readiness for receipt of physical therapy.

Even more radical might be finding a viable alternative to endotracheal intubation and mechanical ventilation, both common reasons why critically ill patients require sedation and analgesia in the ICU. Extracorporeal membrane oxygenation (ECMO) has become an area of increasing interest following its recent successful use for H1N1-associated ARDS [77]. By providing extracorporeal gas exchange, ECMO may mitigate the need for any aggressive mechanical ventilation, and any associated sedation and/or neuromuscular paralysis, in patients with respiratory failure. Indeed, a number of groups have used “awake” ECMO to facilitate rehabilitation and ambulation in critically ill patients awaiting lung transplantation [78–80]. As this technology continues to improve and miniaturize, it is conceivable that mechanical ventilation could eventually be replaced by ECMO, helping clinicians to realize the awake, calm, cooperative, and mobile ICU patient.

**CONCLUSION**

Neuromuscular complications of critical illness are common and can be severe and persistent, with significant impairment in long-term quality of life. While the etiology of ICUAW is multifactorial, both direct (ie, CIP/CIM) and indirect (ie, immobility/disuse atrophy) complications of critical illness contribute to it. Although often cited as important risk factors, there has been conflicting evidence with respect to corticosteroids and neuromuscular blocking agents and the development of ICUAW. Further studies are needed to fully elucidate the mechanisms by which immobility and other aspects of critical illness lead to ICUAW. In addition, longitudinal studies examining the natural history of ICUAW in ICU survivors and the chronic critically ill are needed, as well as a deeper understanding of the associations between the ICUAW, physical function, and quality of life in these patients.
Currently, there are limited interventions to prevent or treat ICUAW, with tight glycemic control having the greatest supporting evidence. Prolonged immobility during critical illness is associated with many detrimental physiological consequences. Emerging data demonstrate the safety, feasibility, and potential benefit of early mobility in critically ill patients with the need for multicenter RCTs to evaluate potential short- and long-term benefits of early mobility and other novel treatments (eg, neuro-muscular electrical stimulation, myostatin inhibitors) on patients’ muscle strength, physical function, quality of life, and resource utilization. Elucidating local barriers, developing guidelines to facilitate early mobilization, advocating for appropriate staffing, and nurturing a culture that prioritizes rehabilitation as an integral part of critical care are important steps in building a sustainable recovery program. Evaluating the ongoing benefits of pro-active rehabilitation as patients transition from the ICU, to the ward, and to the community, would also be of interest. Finally, the putative benefits of early mobilization in other populations of critically ill patients (eg, pediatric, surgical, trauma, neurological) need to be explored in future clinical trials.

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