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ICU-Acquired Weakness

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Survivorship after critical illness is an increasingly important health-care concern as ICU use continues to increase while ICU mortality is decreasing. Survivors of critical illness experience marked disability and impairments in physical and cognitive function that persist for years after their initial ICU stay. Newfound impairment is associated with increased health-care costs and use, reductions in health-related quality of life, and prolonged unemployment. Weakness, critical illness neuropathy and/or myopathy, and muscle atrophy are common in patients who are critically ill, with up to 80% of patients admitted to the ICU developing some form of neuromuscular dysfunction. ICU-acquired weakness (ICUAW) is associated with longer durations of mechanical ventilation and hospitalization, along with greater functional impairment for survivors. Although there is increasing recognition of ICUAW as a clinical entity, significant knowledge gaps exist concerning identifying patients at high risk for its development and understanding its role in long-term outcomes after critical illness. This review addresses the epidemiologic and pathophysiologic aspects of ICUAW; highlights the diagnostic challenges associated with its diagnosis in patients who are critically ill; and proposes, to our knowledge, a novel strategy for identifying ICUAW.   CHEST 2016; 150(5):1129-1140

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Epidemiology of ICU-Acquired Weakness

Neuromuscular abnormalities long have been described in connection with critical illness. In 1892, Sir William Osler reported "rapid loss of flesh" in patients with prolonged sepsis.[1] Mertens[2] described polyneuropathy in patients in a coma in the 1960s; in 1977, evidence of acute myopathy was reported in a patient with status asthmaticus.[3-5] In 2002, De Jonghe et al[6] reported an incidence of ICU-acquired paresis, as measured by means of a Medical Research Council (MRC)-graded manual muscle strength score < 48 (consistent with severe weakness reflecting inability to resist gravity) in 25.3% (24 of 95) of patients receiving mechanical ventilation for ≥ 7 days who survived to awakening and could follow commands. Electrophysiology

(EP) testing performed in all patients with persisting weakness showed reduced compound motor action potentials (CMAPs) and sensory nerve action potentials (SNAPs) with abnormal spontaneous muscle activity—consistent with sensorimotor axonal peripheral neuropathy. Subsequent review of muscle biopsy specimens in 10 patients demonstrated type II fiber atrophy with myosinolysis consistent with primary myopathy and neurogenic muscle atrophy.

These early studies suggest that severe weakness is common in patients who are critically ill, particularly those with prolonged durations of ventilation. Furthermore, objective neuromuscular changes may be more prevalent than is clinically measurable weakness, and studies suggest that these neuromuscular changes may impact outcomes adversely.[7,8] Among 730 patients with respiratory failure, the presence of an abnormal CMAP on day 8 of ventilation was associated with a 20.4% higher 1-year mortality, with a significant difference in the absence of demonstrable weakness (MRC > 48; 1-year mortality, 48.2% [group with abnormal CMAP] vs 29.3%; $P = .010$).[7] Therefore, the impact of these occult neuromuscular changes on longer-term function and outcomes may be greater than previously understood.

Pathophysiology of ICU-Acquired Weakness

ICU-acquired weakness (ICUAW) in patients who are critically ill commonly manifests in three ways: polyneuropathy, myopathy, and/or muscle atrophy.[6] Neuromuscular dysfunction is identified using EP testing. Motor (commonly the peroneal) and sensory (commonly the sural) nerves are stimulated (Fig 1) with increasing stimulus to elicit distal muscle depolarization. Abnormalities in the resultant action potential result from either nerve or muscle injury or a combination of both.

Critical illness polyneuropathy (CIP) is characterized by a symmetric, distal sensory-motor axonal polyneuropathy affecting limb and respiratory muscles, as well as sensory and autonomic nerves.[9-11] EP studies demonstrate abnormal sensory and motor responses with a reduction in the CMAP and SNAP amplitudes. Despite abnormal nerve conduction study (NCS) results, histologic analysis of sensory nerves in patients with CIP generally appear normal early in the course of illness, with axonal degeneration evident only late in the course.[10] Direct muscle stimulation with a stimulating needle electrode demonstrates preserved CMAP
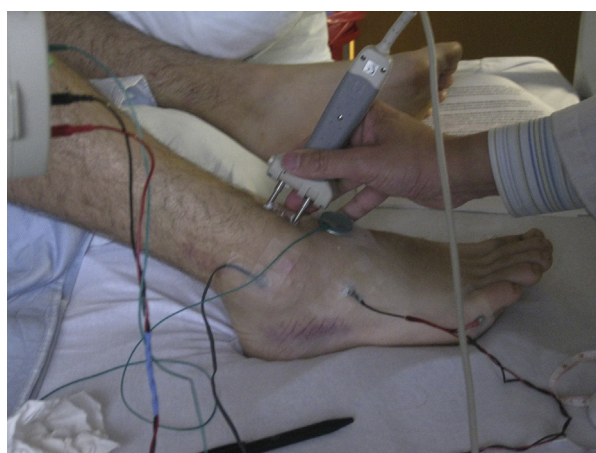

Figure 1 – Single fibular nerve conduction study. In a patient who is supine and normothermic, the recording active electrode (black) is placed over the extensor digitorum brevis muscle. The reference electrode (red) is placed over the fifth metatarsalphalangeal joint. Stimulation occurs 8 cm proximal to the active electrode, slightly lateral to the tibialis anterior tendon. Ground electrode (green) is placed between the stimulation site and the recording active electrode.

amplitude differentiating neuropathy from myopathy. Needle electromyography (EMG) may demonstrate short-term changes associated with axonal loss and reduced recruitment. A number of theories have emerged regarding the cause of the development of CIP, including loss of the blood-nerve barrier, inexcitability of the endoneurial membrane, and direct toxic effects from ICU therapies including hyperglycemia or lipids in parenteral nutrition.[9]

Critical illness myopathy (CIM) is characterized by limb and respiratory muscle weakness with retained sensory function. EP testing demonstrates reduced CMAP amplitudes with preservation of sensory responses. Needle EMG may demonstrate short-term changes and, if the patient is able to participate, myopathic motor unit action potentials. Direct muscle stimulation may demonstrate low-amplitude CMAP from both muscle and nerve. Histologic study of muscle biopsy specimens demonstrates atrophy with preferential loss of thick filaments reflecting myosin loss and muscle necrosis.[10] Proposed causes for the muscle destruction seen in CIM include chemokine-induced autophagy of muscle, muscle membrane inexcitability, acquisition of channelopathies, or direct toxic effects of ICU care including corticosteroids or neuromuscular blockade (NMB).[9]

It is increasingly recognized that muscle atrophy, CIM, and CIP are not necessarily distinct entities but likely are an overlapping spectrum triggered by an acute inflammatory response, often occurring simultaneously.

Therefore, ICUAW phenotypes vary among patients who are critically ill, and ICUAW diagnostic testing relies on varying stages of patient participation, making prevalence studies difficult. These limitations impair our ability to estimate the overall burden of ICUAW precisely in patients who are critically ill.

Current Limitations in Identification of ICUAW

When Bolton et al[12] first described polyneuropathy acquired during critical illness in the early 1980s, they relied heavily on EP testing and muscle biopsy to define the clinical syndromes. Current diagnostic criteria for CIM and CIP require EP testing to demonstrate reductions in CMAPs and SNAPs and histologic evidence for full diagnosis of CIM.[10,13] In reality, at the bedside, performing complete neurophysiologic testing or muscle biopsy in patients who are critically ill remains challenging. The presence of tissue edema and electrical interference theoretically reduces the accuracy of NCSs in

patients in the ICU, although the extent to which these concerns affect diagnosis is unknown. Coagulopathy, lack of trained pathologists for interpretation, cost, and patient refusal because of pain limit the utility of routine muscle biopsy. Additionally, abnormalities may be identified in the vast majority of subjects who are critically ill,[14] suggesting these studies may discriminate poorly between occult and clinically relevant disease.

Given the limitations in specialized diagnostics (Table 1) for ICUAW, investigators have suggested the field should adopt a clinical diagnosis.[15] ICUAW is diagnosed clinically by using a standardized, validated measure such as the manual muscle strength test to quantify muscle weakness. Although strength testing accurately indicates clinically important weakness in up to 25% of patients who are critically ill, a minority of patients (29%) in these studies achieved spontaneous awakening to participate in testing.[6] Identifying patients who are awake and cooperative in the ICU is challenging. Among 135 patients with acute respiratory failure in a

TABLE 1] Benefits and Limitations to Currently Available Modalities for Identifying ICU-Acquired Neuromuscular Dysfunction

Modality	Potential Benefits	Potential Limitations
Full NCSs with EMG	• Part of the gold standard definition of CIM and CIP • Associated with functional outcomes	• Time intensive • Expensive • Moderately invasive • Requires technical expertise • Potentially limited by tissue edema or electrical interference • Requires patient participation for full EMG
Single NCSs	• Quick to perform • Minimally invasive • Less cost than full NCS • Associated with functional outcomes	• Requires technical expertise • Potentially limited by tissue edema or electrical interference
Muscle biopsy	• Depicts muscle architecture • Differentiates CIM from CIP • Part of gold standard for diagnosis of CIM	• Invasive • Expensive • Potentially painful • Requires technical expertise • Requires pathologist support for interpretation • Patient refusal common • Risk of bleeding and/or infection
Muscle ultrasound	• Depicts gross muscle architecture • Noninvasive and comfortable for the patient • Does not require patient participation • Inexpensive once ultrasound machine is obtained • Good interrater reliability • Readily available in most ICU settings	• Requires technical expertise • Diagnostic accuracy and functional significance for CIM and CIP not yet clear • May be limited in patients who are obese or severely edematous
MRC manual muscle strength testing	• Easy to administer • Minimal expertise necessary • Cheap • Direct functional significance	• Relies on patient cooperation • Interrater variation • Ceiling effect after hospital discharge

CIM = critical illness myopathy; CIP = critical illness polyneuropathy; EMG = electromyography; MRC = Medical Research Council; NCS = nerve conduction study.

single center, 75% were unable to participate in MRC testing[16] because of coma, delirium, and traumatic injury early in the course of critical illness. Beyond patient participation, there is significant interobserver variation in the MRC scale. A study of manual muscle strength testing by two experienced physiotherapists showed only moderate interobserver agreement (κ, 0.60).[17] In a cohort restricted to patients who were cooperative, MRC testing performed better, with very good interobserver agreement (intraclass correlation, 0.95) when performed by trained physiotherapists.[18] However, these concerns limit routine MRC manual muscle strength testing in the diagnosis of ICUAW, particularly early in the course of critical illness.

Some studies propose that handgrip strength measured by means of handgrip dynamometry may be useful as an alternative measure of global muscle strength in patients who are critically ill. In a prospective study of patients with respiratory failure, dynamometry helped diagnose ICUAW with a sensitivity of 80.6%, specificity of 82.4%, and negative predictive value of 91.3% when compared with MRC testing as a gold standard.[19] This study also showed a significant independent association between low handgrip strength and mortality. However, such studies are limited by the same aforementioned limitations given the use of the MRC scale as the gold standard comparison, making the exact role of handgrip dynamometry uncertain.

Additional Diagnostic Approaches to Identify ICUAW

Prompt, routine diagnosis of ICUAW in patients who are critically ill is hindered by the absence of a reliable, easily obtainable screening test in patients who are comatose. EP assessment and muscle biopsy are not employed routinely in clinical practice, and manual muscle strength testing requires a patient who is participatory. Studies of incidence, risk factors, and outcomes of ICUAW are impaired by the inability to make consistent diagnoses.

Limited NCSs show promise as a sole diagnostic test for ICU-acquired neuromuscular dysfunction.[8] This test is quick, safe, and easy to administer. The common peroneal (fibular) CMAP is measured using two surface electrodes, with the active electrode placed on the belly of the extensor digitorum brevis muscle and the reference electrode placed on the distal tendon of the recorded muscle (Fig 1).[20] The peroneal nerve is stimulated over the dorsum of the foot near the ankle,

with increasing stimulus intensity until maximal CMAP is achieved. Latronico et al[20] validated this procedure in a multicenter cohort of patients who were critically ill. Comparing single peroneal NCS with complete NCS-EMG studies, the single nerve study was 100% sensitive (95% CI, 96.1%-100%) for the diagnosis of polyneuropathy and myopathy, with a specificity of 85.2% (95% CI, 66.3%-95.8%). Similarly, Moss et al[8] reported that peroneal and sural sensory NCS yielded a sensitivity of 100% (95% CI, 100%-100%; c-statistic, 0.9336) for neuromyopathy, with a specificity of 81% (95% CI, 71%-91%). Diagnostic accuracy appears improved with the use of cutoffs derived from subjects with ICUAW rather than healthy control subjects (specificity of 75% in ICUAW vs 36% in healthy control subjects).[21] These results suggest that isolated lower extremity NCS may be adequate for diagnosis of ICUAW. Although EP studies may be useful in the diagnosis of ICUAW, therapeutic utility is limited. Currently, no therapeutic options for ICUAW exist that alter EP findings, making it unlikely that routine use in clinical care would impact routine outcomes.

Point-of-care ultrasound is an essential diagnostic tool in modern ICUs, and quantitative neuromuscular ultrasound increasingly is being evaluated as a research tool for identification of muscle atrophy.[22] In a study of 63 patients who were critically ill, cross-sectional area measurement by means of ultrasound of the rectus femoris muscle demonstrated early, rapidly progressive muscle loss averaging a 10% loss in cross-sectional area over the first week of respiratory failure.[23] In another cohort of patients with respiratory failure, vastus lateralis ultrasound had a sensitivity of 74% for prediction of myofiber necrosis in muscle biopsy specimens; in patients without a potential iatrogenic cause for muscle necrosis, sensitivity increased to 85%.[24] Among patients with sepsis, muscle ultrasound was able to help detect neuromyopathy in 93% of patients studied, with excellent interrater reliability (intraclass correlation, 0.97).[24] Although muscle ultrasound is a potential noninvasive marker of ICUAW, we currently lack evidence demonstrating an association between ultrasound findings and clinical outcomes and therapeutic ultrasound targets, limiting routine clinical use.

Risk Factors for Development of ICUAW

Premorbid Health as a Potential Risk Factor

To date, most studies of weakness, atrophy, myopathy, and neuropathy seen during and after critical illness

make the assumption that these abnormalities are ICU acquired, stemming from direct effects of critical illness or sequelae of short-term interventions. However, studies of ICUAW are limited by a lack of baseline neuromuscular assessment, and, to our knowledge, no studies to date attempt to control for prehospital muscle function or overall functional status as a predictor of ICUAW.

Sarcopenia is the age-related loss of muscle mass constituting part of the frailty syndrome, a complex disease process characterized by loss of cognitive and physical reserve in elderly adults.[25] Investigations suggest that up to 81% of elderly patients in the ICU, in the absence of known ICUAW, met frailty criteria.[26] Patients who were frail and older experienced a threefold increase in ICU mortality and an increased risk of death in the 6 months after critical illness.[27] In nonelderly individuals, clinically defined frailty was associated with an 80% increase in the odds of in- and posthospital (< 6 months) death, with an increasing frailty score correlating with death in a linear dose-response fashion.[26] In patients surviving critical illness, frailty appears to be an important predictor of long-term morbidity.[26,28] Patients with identified frailty who survived critical illness were 22% less likely to be living at home independently during the year after critical illness and reported significantly worse health-related quality of life than did nonfrail survivors of critical care or the general population.[26,28] Studies are needed that examine the role of frailty specifically in subjects with known ICUAW to understand its impact on ICUAW outcomes.

In studies of survivors of severe sepsis with available prehospital data, pre-illness function was an independent predictor of incremental loss in function and associated cognitive decline.[29] Analysis of patients with years of prehospital functional data subsequently admitted for severe sepsis demonstrated that many of the symptoms of the post-ICU syndrome commonly were present before admission.[30] Accounting for the prehospital functional trajectory appeared to define the care trajectory after critical illness better.[30] These data highlight the increasing recognition that prehospital function informs in- and posthospital impairments and the variance in ICUAW phenotypes that may respond differentially to ICU interventions.

In-Hospital Risk Factors for ICUAW

Despite dozens of studies looking at clinical risk factors for ICUAW, there is still little certainty of which factors

are truly causal. The most consistently implicated risk factors are those associated with severity of illness, including shock, sepsis, and degree of multiple organ failure.[6,20,31,32] This supports the premise that ICUAW is actually another manifestation of the multiple organ dysfunction syndrome.[31,33] Cohort studies in patients who are critically ill show an association between sepsis and ICUAW in unadjusted analyses with estimated ORs varying between 2.9 and 49.[15]

A number of ICU interventions or exposures are identified as potential risk factors for ICUAW. These include administration of corticosteroids or NMB, glycemic control, aminoglycoside therapy, and immobilization. There are conflicting data on the associations between corticosteroids and NMB with ICUAW.[6,34-40] Unadjusted analyses[4,34,40] in patients who are critically ill suggest an increased frequency of ICUAW in patients receiving corticosteroids, and a single multivariable analysis reported increased risk of paresis in patients exposed to steroids (OR, 14.90; 95% CI, 3.20-69.80; $P < .001$).[6] Additional multivariable analyses including one randomized controlled trial (RCT) secondary analysis, however, failed to show an association between corticosteroids and ICUAW.[31,33,41] The overall effect of corticosteroids on ICUAW remains uncertain and difficult to ascertain because of indication bias, high variability in patient phenotypes, and steroid dosing. Although steroids act as direct nerve and muscle toxins, they also are associated with reduced inflammation and severity of illness, which may decrease risk for ICUAW. Likewise, small unadjusted analyses suggest increased frequency of ICUAW in patients receiving NMB agents.[37,42] Adjusted analyses, however, failed to show an independent association of NMB with development of ICUAW,[6,31] and a single RCT of early NMB use in patients with ARDS showed no significant difference in development of ICUAW.[43] Like steroids, early NMB may result in decreases in other better established risk factors, including severity of illness or organ dysfunction and duration of mechanical ventilation.

In an RCT, intensive insulin therapy decreased abnormal spontaneous activity at EMG, suggesting that more insulin and less hyperglycemia may reduce ICUAW.[44] Aminoglycoside antibiotics were associated with paresis in a single study; however, additional observational studies demonstrated no significant association.[6,34,36,39,40] There are single studies suggesting that other potentially modifiable ICU interventions, including liberal fluid administration and transfusion,

may contribute to ICUAW, although these associations need verification in larger patient cohorts.[45,46]

Prolonged immobilization is associated with atrophy in patients who are critically ill. Muscle disuse is associated with changes in muscle diameter, length, and contractile strength.[47-50] These changes may result in increasing muscle atrophy as the duration of immobility is prolonged. In healthy subjects, muscles show sarcomere reduction and fiber shortening within 4 hours of immobilization.[47,48] After 1 week of complete immobilization in healthy volunteers, postural muscle strength is reduced by 5% to 10%, with an average daily loss of 1% to 1.3% of overall muscle strength.[51,52] This reduction may be exacerbated further by critical illness. In an observational cohort of 109 patients with ARDS, survivors experienced 18% reductions in their baseline body weight on average at hospital discharge.[53] Immobilization, therefore, may be an early identifiable, modifiable risk factor for targeted interventions. Studies are needed to determine whether identification and modification of such risk factors early in the course of critical illness contributes to reductions in prevalence of ICUAW.

ICUAW, Mortality, and Long-term Physical Function

An increasing number of studies highlight the burden of impairment seen after critical illness, particularly after ARDS, but few attempt to link ICUAW with subsequent morbidity and mortality. ICUAW is an increasingly recognized independent predictor of mortality in patients who are critically ill. In a propensity-matched cohort of patients who were critically ill, MRC-defined ICUAW was associated with a 30% lower likelihood of being alive at hospital discharge (hazard ratio, 0.70; 95% CI, 0.55-0.86; P = .008), with a 13% increase in mortality at 1 year.[54] This finding supports those of prior observational studies, suggesting increased odds of death associated with ICUAW independent of other ICU factors.[19,55]

Although it seems intuitive that ICUAW would impact long-term physical function after critical illness, few data support this assumption to date. In the Improving Care of Acute Lung Injury Patients study, Fan et al[56] examined the association between ICUAW (defined as an MRC strength score < 80% maximum) with postdischarge strength measured by means of serial testing at 3, 6, 12, and 24 months after ARDS. In the cohort, 36% of patients exhibited signs of ICUAW at

hospital discharge, with the prevalence decreasing to 22% at 3 months, 15% at 6 months, 14% at 12 months, and 9% at 24 months after ARDS.[56] Manual muscle strength increased significantly over time, with an increase in total MRC score from 50 at hospital discharge to 57 at 24 months.[56] Despite improvements in overall strength, physical functioning health-related quality-of-life subscales remained significantly lower than age-adjusted norms at all time points, achieving only 72% of baseline values at 24 months.[56] Patients with documented ICUAW maintained significantly worse handgrip strength and reported worse physical functioning health-related quality of life.

Similarly, in a cohort of survivors of critical illness, Wieske et al[57] noted that patients receiving mechanical ventilation who developed MRC-defined ICUAW experienced significantly lower physical functioning health-related quality of life (median Short-Form 36 [SF-36] Physical Functioning Score [PFS] of 45 [interquartile range, 30-79] vs 75 [interquartile range, 50-90]; P ≤ .01) compared with patients who were not weak at 6 months after illness. Higher strength scores were correlated significantly with higher PFS. ICUAW was associated with a 16.7-point decrease in PFS after covariate adjustment.[57] Further studies are needed to understand the long-term impact of ICUAW on the burden of impairment seen after critical illness.

Interventions Aimed at Reducing ICUAW

Therapeutic options for prevention or treatment of ICUAW remain limited. Table 2 presents a summary of prevention and intervention studies in patients with or at risk for ICUAW. Secondary analyses of an RCT of intensive insulin therapy (blood sugar levels between 80 and 110 mg/dL) suggested more stringent glucose control was associated with lower rates of ICUAW. Intensive insulin therapy, however, also was associated with increased rates of life-threatening hypoglycemia, leading most clinicians to abandon the practice.[44,59]

There is building literature regarding early exercise to maintain muscle strength and improve function in patients in the ICU. Prospective cohort studies in patients with acute respiratory failure showed that mobility in patients receiving mechanical ventilation was safe, feasible, and associated with reductions in length of stay and mortality.[61,66-68] An RCT in patients performing activity through physical or occupational therapy within 48 hours of respiratory failure showed improvement in activities of daily living (ADLs)

TABLE 2] Summary of Interventions Aimed at Reducing ICU-Acquired Neuromuscular Dysfunction

Study/Year	Study Design/Cohort	Interventions	Outcomes
Griffiths et al[58]/1995	Prospective cohort study in patients receiving neuromuscular blockade for > 7 days (n = 5)	Between-leg comparison of 3-h continuous passive motion daily with no therapy	11% mean increase in fiber area
van den Berghe et al[44]/2001	Prospectively planned subgroup analysis of RCT (n = 1,200)	Intensive insulin vs standard insulin therapy	Decrease in critical illness polyneuropathy by 49%, increase in life-threatening hypoglycemia
Hermans et al[59]/2009	Secondary analysis of RCT in patients requiring at least 7 days of mechanical ventilation (n = 420)	Intensive insulin therapy vs standard insulin therapy	Reduction in critical illness polyneuropathy of 11.6%
Burtin et al[60]/2009	RCT in patients who were critically ill with expected stay of 7 days (n = 90)	20-min bedside ergometer use vs usual care	Greater 6MWD, SF-36 physical functioning score, and quadriceps force at hospital discharge
Morris et al[61]/2008	Prospective cohort study in patients with acute respiratory failure in the medical ICU (n = 330)	Progressive mobility protocol vs usual care	Reduction in ICU and hospital length of stay
Schweickert et al[62]/2009	RCT in patients with acute respiratory failure in the medical ICU (n = 104)	Early physical and occupational therapy vs usual care	Increase in ambulation status and activities of daily living independence, reduction in delirium and in ICU and hospital length of stay, trend toward improved muscle strength
Angelopoulos et al[63]/2013	RCT in patients who were critically ill with and without neuromyopathy (n = 31)	Neuromuscular stimulation using high (75 Hz) or medium (45 Hz) frequency for 30 min	Increased oxygen consumption, endothelial reactivity, and vascular reserve
Kho et al[64]/2015	RCT in patients in the medical ICU (n = 36)	Neuromuscular stimulation applied to three lower extremity muscle groups for 60 min compared with sham	Greater walking distance, trend toward increased muscle strength according to MRC
Dirks et al[65]/2015	Prospective cohort study in patients who were comatose (n = 6)	Neuromuscular stimulation to one leg twice daily for 7 days compared with no stimulation	No atrophy in stimulated leg, muscle mRNA upregulation

6MWD = 6-min walk distance; RCT = randomized controlled trial; SF-36 = Short-Form 36. See Table 1 legend for expansion of other abbreviations.

independence (59% vs 35%; $P = .02$) and a greater walking distance at hospital discharge (33.4 vs 0 m; $P = .004$) for patients in the intervention group.[62] There was a nonstatistically significant trend toward reductions in ICUAW ($P = .09$), although the study was underpowered for this end point.[62] A meta-analysis of the RCTs of early mobilization suggests it may be an effective treatment for ICUAW (pooled effect OR, 0.27; $P = .03$).[69]

Patients who are critically ill rarely are mobilized, with studies suggesting that less than 10% of patients receiving mechanical ventilation receive out-of-bed mobility while in the ICU.[70,71] Studies of in-bed cycling or direct muscle stimulation in patients who are comatose show promising results for reducing the

burden of ICUAW, but these methods are still not proven effective. An RCT randomized 90 patients who were critically ill to a 30-minute session of cycle ergometry, either as passive cycling for patients who were comatose or active cycling for patients who were participating, or to standard rehabilitation care in the control group; results in the cycling group were greater walk distances and quadriceps force, with greater physical functioning quality-of-life scores at hospital discharge.[60] Similarly, an RCT in 36 patients undergoing daily neuromuscular stimulation to the quadriceps, gastrocnemius, and tibialis anterior with a pulsed current and a biphasic, asymmetric, balanced rectangular waveform, with a ramp-up time of 2 seconds, ramp-down time of less than 1 second, and frequency (pulse rate) of 50 Hz resulted in longer

walk distances and a trend toward increased muscle strength.[64] Studies are needed to confirm these results in larger cohorts and to define better the appropriate timing, dosing, and frequency of cycle ergometry; functional neuromuscular stimulation; and ICU mobility for patients who are critically ill.

A number of ongoing trials are exploring potential preventive pharmacologic agents for ICUAW. These agents are primarily antiinflammatory or metabolic agents aimed at lessening the prevalence of ICUAW. Preventive therapies currently in active trials include serotonin 5-HT2C receptor agonists, hydroxymethylbutyrate and eicosapentaenoic acid, and intravenous immunoglobulin (NCT02523690, NCT01270516, NCT01867645). Additional agents aimed at lessening the severity of ICUAW once present are also in drug development.

Interventions Aimed at Treating ICUAW

Once patients have developed ICUAW, it would be of use to know which interventions are most likely to restore previous function. Unlike other conditions associated with significant impairment—such as stroke, traumatic brain injury, or spinal cord injury—the exact type of rehabilitation interventions required to reduce impairment, maximize functional independence, and improve health-related quality of life are not yet well understood. To date, limited studies have evaluated intensive inpatient-based and outpatient rehabilitation programs.

One observational cohort study evaluating comprehensive inpatient rehabilitation in patients with CIM or CIP identified improvements in motor functional independence measures (mean increase from 45.6 to 69.7) and functional independence measures (mean increase from 78.7 to 103.3) between admission and discharge with mean stay of 67.4 days.[72] Similarly, mean 6-minute walk test results improved from 77.3 to 291.5 m, and mean 10-m walk test results improved from 1.5 to 2.4 km/h, but this study was limited by a lack of control subjects and overall methodologic quality.[72] A 2010 RCT studying the effects of dedicated geriatric ward care on outcomes in elderly survivors of the medical ICU with unknown ICUAW status failed to demonstrate a significant difference in functional indexes (ie, Barthel index) after hospital discharge (75.6 vs 64.6; $P = .2$).[73] An RCT of a home-based physical rehabilitation program with 195 participants also noted no significant effect in the SF-36 PFS or 6-minute walk test at 1, 8, or 26 weeks after hospital discharge, although this cohort was not restricted to

patients who were weak.[74] However, randomization to receipt of a 6-week self-help rehabilitation manual was associated significantly with improvements in the SF-36 PFS at 8 weeks and 6 months ($P = .006$), with a trend toward a lower rate of depression at 8 weeks (12% vs 25%).[75]

Randomized studies to date have not evaluated more comprehensive inpatient or outpatient rehabilitation programs employing occupational, physical, and speech or cognitive therapies; swallow evaluation; architectural accessibility and home modification; adaptive mobility and ADL devices; vocational rehabilitation; rehabilitation psychology; and therapeutic recreation. On the basis of models used for other conditions,[76,77] it is likely that patients with physical and cognitive impairments following an ICU stay could benefit from comprehensive rehabilitation with interventions directed at addressing each of these domains. Additionally, it would be of use to evaluate the effect of these interventions on mortality, hospital readmission rates, required caregiving, health-related quality of life, and return to work or school.

A Staged Approach to Classifying ICUAW

Throughout this review, we have highlighted the heterogeneity of ICUAW, the difficulty with its routine diagnosis, and our current lack of effective therapies for reversing disease. Given these difficulties, we submit that a one-size–fits-all approach to diagnosing and treating ICUAW may not be an effective strategy. Although certain elements such as risk factor avoidance or modification potentially may be beneficial to all patients in the ICU, we suggest that, in general, assessments and interventions should target individualized stages of disease along the spectrum of dysfunction. Therefore, we propose the following theoretical framework (Fig 2) as a guide for future research on ICUAW.

Critical illness and recovery can be conceptualized as spanning four stages: stage 0, pre-ICU: baseline functional assessment and prehospital trajectory; stage 1, early ICU: assessment of the patient who is not participatory; stage 2, late ICU: strength and function assessment; and stage 3, post-ICU: recovery assessment. Assessment modalities and instruments should be geared toward the targeted phase and potential patient participation. Interventions targeting ICUAW, alternatively, should not be restricted to a single stage, but rather stages should guide the development of interventions along the continuum.
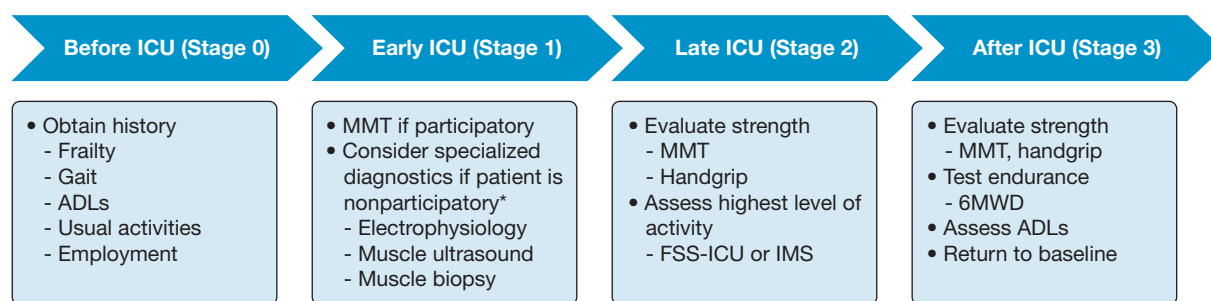
Before ICU (Stage 0)	Early ICU (Stage 1)	Late ICU (Stage 2)	After ICU (Stage 3)

• Obtain history
  - Frailty
  - Gait
  - ADLs
  - Usual activities
  - Employment
	• MMT if participatory
	• Consider specialized diagnostics if patient is nonparticipatory*
	  - Electrophysiology
	  - Muscle ultrasound
	  - Muscle biopsy
		• Evaluate strength
		  - MMT
		  - Handgrip
		• Assess highest level of activity
		  - FSS-ICU or IMS
			• Evaluate strength
			  - MMT, handgrip
			• Test endurance
			  - 6MWD
			• Assess ADLs
			• Return to baseline

Figure 2 – *Proposed staged approach to diagnosis and treatment of ICU-acquired weakness. 6MWT = 6-min walk test; ADLs = activities of daily living; FSS-ICU = functional status score for the ICU; IMS = ICU Mobility Scale; MMT = manual muscle testing. *Note that many patients in the ICU will remain participatory and skip stage 1. Also note that specialized diagnostics are not recommended as standard clinical practice but rather for research or for evaluation of distinct clinical questions.*

The initial evaluation begins with a detailed baseline functional history. This stage focuses on in-depth understanding of the prehospital functional status. Key components of this functional history include data on basic and instrumental ADLs, locomotion status including fall history, employment or education, and cognitive status. This stage may use additional constructs, such as frailty, as a means of quantifying prehospital disability, functional trajectory, and resilience. Integrated electronic health record symptoms that allow for enhanced outpatient functional screening for the aforementioned domains may facilitate construction of detailed functional trajectories.

In the first stage of ICU assessment, many patients will be unable to participate. Clinicians should employ best practice methods for reducing delirium, including minimization of delirium-inducing medications, maintenance of sleep-wake cycles, and family engagement to optimize participation. Patients awake enough to participate should undergo strength testing by using a validated strength scale. Given the current lack of targeted therapy for ICUAW, further diagnostic testing may have limited clinical utility at this stage, and extensive diagnostics are not recommended as standard practice.[78] However, patients with atypical clinical presentations for ICUAW (focal neurologic findings, distal weakness) or with underlying neurologic injury impacting strength testing may benefit from additional testing to exclude alternate causes or confirm the diagnosis of ICUAW (eg, patients with stroke or spinal cord disease who develop additional risk factors for ICUAW).[79] For research studies, we propose EP assessment, preferably using a single nerve protocol, early in the course of critical illness. Interventions at this time may include antiinflammatory or metabolic agents aimed at reducing neuromuscular injury, early risk factor modification to reduce severity of disease, and

potentially cycle ergometry with functional electrical neuromuscular stimulation when active mobilization participation is not possible.

Once a patient is able to participate, assessments shift toward stage 2, focused on the delineation of newly acquired functional impairments so that a comprehensive rehabilitation plan can be designed. Strength can be assessed using validated, easy-to-use tests, including handgrip dynamometry and/or manual muscle strength testing. Global measures of strength at this time would include instruments created and validated for patients in the ICU such as the functional status score for the ICU (e-Appendix 1). The functional status score for the ICU is widely available (http://www.hopkinsmedicine.org/pulmonary/research/outcomes_after_critical_illness_surgery/oacis_instruments.html), easy to administer, easy for the patient to complete, and responsive to change.[80,81] Functional assessment should focus on the same domains as in stage 0—namely, basic and instrumental ADLs, ambulation status, and cognitive status. Interventions at this time should focus on addressing the identified strength or functional deficits and may include aggressive physical and occupational therapy interventions or anabolic interventions.

As a patient shifts into the recovery phase (stage 3) of critical illness, the intensity of global assessments increases. The Physical Function ICU Test (PFIT) was designed to measure strength, endurance, cardiovascular capacity, and functional level in patients who are critically ill.[82,83] The PFIT correlates moderately with objective measures of muscle strength, including the Timed Up and Go test ($r = -0.6$), 6-minute walk test ($r = 0.41$), and MRC muscle test ($r = 0.49$) and is responsive to change in patients who are critically ill.[82] In a cohort of 66 survivors of the ICU, the PFIT

demonstrated excellent validity with MRC tested muscle strength ($r = 0.8$), was predictive of discharge to home, and demonstrated moderate responsiveness to change.[81] At this point, interventions shift toward acceptance of newfound impairment while attempting to optimize function as much as possible. Further studies are needed to understand how factors associated with disability adaptation, including coping, mindfulness, and resiliency, or how alterations of the built or social environment impact recovery after critical illness.[84,85]

Conclusions

ICUAW is common in patients who are critically ill, often is underreported, and manifests in a spectrum of disease. Diagnostic limitations in our current testing modalities limit identification of weakness early in critical illness. Although illness severity, multiorgan failure, and immobilization are recognized as potential risk factors for ICUAW, the strength of these associations remains uncertain. Adjustment for baseline function may play an important role in understanding disease trajectories for ICUAW. To our knowledge, novel diagnostic methods, including single NCS and muscle ultrasound, may provide a minimally invasive means for early recognition of disease. Risk factor avoidance or modification and early activity may reduce the risk and severity of ICUAW. Studies are needed that explore interventions targeted toward patient participation and stage of disease rather than being applied uniformly across the spectrum.

Acknowledgments

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