



An Official American Thoracic Society Clinical Practice Guideline: The Diagnosis of Intensive Care Unit–acquired Weakness in Adults

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Rationale: Profound muscle weakness during and after critical illness is termed intensive care unit–acquired weakness (ICUAW).

Objectives: To develop diagnostic recommendations for ICUAW.

Methods: A multidisciplinary expert committee generated diagnostic questions. A systematic review was performed, and recommendations were developed using the Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Measurement and Main Results: Severe sepsis, difficult ventilator liberation, and prolonged mechanical ventilation are associated with ICUAW. Physical rehabilitation improves outcomes in heterogeneous populations of ICU patients. Because it may not be feasible to provide universal physical rehabilitation, an alternative approach is to identify patients most likely to benefit. Patients with ICUAW may be such a group. Our review identified only one case series of patients with ICUAW who received physical therapy. When compared with a case series of patients with ICUAW who did not

receive structured physical therapy, evidence suggested those who receive physical rehabilitation were more frequently discharged home rather than to a rehabilitative facility, although confidence intervals included no difference. Other interventions show promise, but fewer data proving patient benefit existed, thus precluding specific comment. Additionally, prior comorbidity was insufficiently defined to determine its influence on outcome, treatment response, or patient preferences for diagnostic efforts. We recommend controlled clinical trials in patients with ICUAW that compare physical rehabilitation with usual care and further research in understanding risk and patient preferences.

Conclusions: Research that identifies treatments that benefit patients with ICUAW is necessary to determine whether the benefits of diagnostic testing for ICUAW outweigh its burdens.

Keywords: critical care; intensive care unit–acquired weakness; diagnosis; definitions; critical illness polyneuropathy; critical illness myopathy; critical illness myoneuropathy

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Overview

Severe muscle weakness is common among critically ill patients, yet there is no consensus on whether or how to systematically identify patients with intensive care unit–acquired weakness (ICUAW). The guideline development committee began with a systematic review that identified that ICUAW may be more common among ICU patients with severe sepsis as well as those having difficulty being liberated from mechanical ventilation or requiring prolonged mechanical ventilation.

Literature review failed to identify evidence comparing the effects of diagnostic testing versus no diagnostic testing on clinical outcomes. A small case series of patients with ICUAW who received physical therapy was identified, and when compared with a similar series of patients with ICUAW who did not receive physical therapy, it appeared that therapy patients might be discharged home rather than to a rehabilitative facility more frequently. However, the confidence intervals did not exclude no effect. As such, the evidence provides very little confidence in the estimated effects of physical therapy on clinical outcomes in patients with ICUAW. The guideline development committee is certain that additional research is necessary to determine whether intervention improves outcomes in patients with ICUAW, and such evidence is necessary before deciding whether or not routine diagnostic testing for ICUAW is indicated.

Testing for and treatment of ICUAW is a promising management strategy for which, thus far, there is insufficient evidence of benefit to support its use. The committee members believe that further research has the potential for reducing uncertainty about the effects of this management strategy and that the results of such research will be of good value for the anticipated costs. Therefore, to recommend a diagnostic approach to testing for ICUAW, the committee made the following recommendations (Table 1).

Recommendation 1: We recommend well-designed, adequately powered and executed randomized controlled trials comparing physical rehabilitation or other alternative treatments with usual care in patients with ICUAW that measure and report patient-important outcomes.

(strong recommendation, very low-quality evidence)

Recommendation 2: We recommend clinical research to determine the role of prior patient disability in the development of and recovery from ICUAW. (strong recommendation, very low-quality evidence)

Recommendation 3: We recommend clinical research that determines whether or not patients would want to know if they have ICUAW even though no specific therapy currently exists and how patient preferences influence medical decision making or the perception of prognosis. (strong recommendation, very low-quality evidence)

Introduction

It is estimated that 13 to 20 million people annually require life support in intensive care units (ICUs) worldwide (1). In the United States, more than 750,000 people receive mechanical ventilation (2, 3), with almost 300,000 requiring prolonged support (>5 d) annually (3–6). Physical impairment is common in this patient group and may persist for years (7–11). In some patients, physical deficits manifest as profound weakness (12), which is associated with worsened outcomes (7, 13). Multiple series estimate that ~25% of patients who require prolonged mechanical ventilation develop global and persistent weakness (7, 8). Based on this, more than 75,000 patients in the United States and up to 1 million worldwide may develop the syndrome of global weakness termed ICU-acquired weakness (ICUAW).

ICUAW is caused by a variety of different pathologies, including critical illness myopathy, polyneuropathy, or a combination (12, 14). It can lead to prolonged mechanical ventilation (15–17) and hospital stay (7, 8) and increased mortality (7, 13). Many patients recovering from critical illness report physical symptoms that persist for years (10, 11), suggesting they may have experienced ICUAW acutely (18, 19).

Rehabilitative therapy improves short-term patient-centered outcomes in heterogeneous populations of ICU patients (20, 21). Because it may not be feasible in many centers to provide early physical and occupational therapy to all ICU patients (22, 23), an alternative approach

is to identify subtypes of ICU patients who are most likely to benefit from these therapies. Patients with ICUAW may be such a subtype according to very low-quality evidence (7, 8, 24). Initiation of early rehabilitation or an alternative potentially beneficial therapy (25–27) is not the only reason to identify ICUAW, however. A diagnosis of ICUAW prevents unnecessary testing for alternative diagnoses (28) and improves the accuracy of counseling about the anticipated duration of mechanical ventilation and the appropriate timing for transition from intensive to rehabilitative care (11, 19, 23, 29–31).

There is no consensus approach to the diagnosis of ICUAW, including how or when the diagnosis can be made (12, 14, 32). It is also uncertain how electrophysiological studies should be used. To address such uncertainties, a panel was convened in March of 2009. The panel organized the disparate terms and standards used to describe ICUAW and introduced a clinical approach (12). Using the panel's work as our framework (12, 33, 34), we convened a committee to generate specific recommendations about the diagnosis of ICUAW. We asked specific clinical questions, prioritized outcomes, developed an *a priori* search strategy and selection criteria, and then performed a systematic review of the literature. The literature was appraised using the Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach and then used to formulate and grade clinical recommendations.

Methods

The methods used to develop these guidelines are summarized in Table 2.

Guideline Panel

These guidelines were developed using the GRADE approach in accordance with American Thoracic Society (ATS) policies (35, 36). The Critical Care and Nursing Assemblies of the ATS sponsored the project. Invitations were sent out by the committee chair (N.A.A.) and planning committee (D.M.N. and Roy G. Brower) to an initial list of experts who were asked for nominations. Twenty-two individuals accepted, representing multiple stakeholder

Table 1. Recommendation to Aid in Decisions Regarding Diagnostic Testing for Intensive Care Unit–acquired Weakness

Recommendation	Remarks	Values and Preferences
<ol style="list-style-type: none"> 1. We recommend well-designed, adequately powered and executed randomized controlled trials comparing physical rehabilitation or other alternative treatments with usual care in patients with ICUAW that measure and report patient-important outcomes. (strong recommendation, very low-quality evidence) 2. We recommend clinical research to determine the role of prior patient disability in the development of and recovery from ICUAW. (strong recommendation, very low-quality evidence) 3. We recommend clinical research that determines whether or not patients would want to know if they have ICUAW even though no specific therapy currently exists and how patient preferences influence medical decision making or the perception of prognosis. (strong recommendation, very low-quality evidence) 	<p>The recommendations are strong because the guideline development committee is certain that additional research is necessary to prove whether physical rehabilitation or other interventions improve outcomes in patients with ICUAW, and such evidence is necessary before deciding whether or not routine diagnostic testing for ICUAW is indicated.</p>	<p>These recommendations place a higher value on avoiding potentially burdensome diagnostic testing if it will not lead to improved outcomes and a lower value on an uncertain improvement in the rate of discharges home rather than to a rehabilitative facility.</p>

Definition of abbreviation: ICUAW = intensive care unit–acquired weakness.

disciplines from North America and Europe. Four individuals could not participate, and two members (committee chair [N.A.A.] and academic librarian [F.C.]) were excluded from voting, leaving 16 voting members (*see* Table E1 in the online supplement).

Formulation of Questions and Definition of Important Outcomes

The guideline development committee met to discuss the primary findings from the prior panel (12), review diagnostic issues in ICUAW, and identify important clinical questions (Table 3). The committee discussed what potential benefits patients could experience if an accurate diagnosis was made. Critical beneficial outcomes (i.e., outcomes that alone are sufficient to warrant diagnostic testing) included improved survival or reduced recovery time, with the latter indicated by a shorter duration of mechanical ventilation, reduced length of stay in the ICU or hospital, and/or discharge home rather than to a rehabilitative or long-term medical facility. Less important beneficial outcomes included reduced patient or family anxiety due to incorrect expectations about recovery, more accurate counseling about forthcoming needs for ventilation and rehabilitative services (10, 11, 19), and less unnecessary testing to determine the

cause of delayed ventilator liberation or perceived coma (28). The committee also identified the downsides of diagnostic testing. For manual muscle testing (MMT), the burden of performing a more extensive physical examination and the possibility of inconclusive results from patient or practitioner factors were the identified downsides. For electrophysiological testing, potential downsides included incorrect prognostic expectations for false-positive results and both unnecessary diagnostic uncertainty and delayed initiation of therapy for false-negative results.

Systematic Review

A systematic literature review developed the bibliography for the guideline development process. A single search strategy was used, because each of the questions is related to the diagnosis of ICUAW. A sensitive search strategy was developed by the committee’s medical librarian (F.C.), which combined Medical Subject Headings and various keywords (37). The search strategy shown in Table E2 was initially performed in March of 2009 and then was periodically updated during the development of the guideline. Two panelists (E.F. and N.A.A.) selected relevant studies using the following inclusion criteria: (1) randomized clinical trial, observational study, or case series

(enrolling three or more patients); (2) exclusive enrollment of patients aged 18 years or older; and (3) explicit reporting of diagnostic testing for ICUAW. Disagreement was adjudicated through consensus of the same reviewers. The same two panelists examined the bibliographies of the selected articles and related reviews for additional studies, reviewed the studies, extracted crude data, and appraised the quality of each article.

Developing Recommendations

Recommendations were considered based on the balance of beneficial versus adverse outcomes, quality of evidence, burdens, costs, and patient preferences. If it was unclear whether a particular course of action was favorable or unfavorable even after weighing these factors collectively, a recommendation was made for further research

Results

Definition

ICUAW is a syndrome of generalized limb weakness that develops while the patient is critically ill and for which there is no alternative explanation other than the critical illness itself (12). There is no universally accepted reference standard for

Table 2. Methods Checklist

	Yes	No
Panel assembly		
Included experts for relevant clinical and nonclinical disciplines	X	
Included individual who represents the views of patients and society at large		X
Included a methodologist with appropriate expertise (documented expertise in conducting systematic reviews to identify the evidence base and the development of evidence-based recommendations)	X	
Literature review		
Performed in collaboration with librarian	X	
Searched multiple electronic databases	X	
Reviewed reference lists of retrieved articles	X	
Evidence synthesis		
Applied prespecified inclusion and exclusion criteria	X	
Evaluated included studies for sources of bias	X	
Explicitly summarized benefits and harms	X	
Used GRADE to describe quality of evidence	X	
Generation of recommendations		
Used GRADE to rate the strength of recommendations	X	

Definition of abbreviation: GRADE = Grading, Recommendations, Assessment, Development, and Evaluation.

ICUAW. The various definitions available in the literature were considered, and their merits were discussed. The Medical Research Council (MRC) muscle strength score was used in the majority of studies reporting strength. As a result, in these guidelines, we consider the reference standard to be an average MRC muscle strength score of less than 4 across all muscles tested as determined by MMT (7).

Summary of Evidence

The initial search, excluding duplicate reports from multiple databases based on title, identified 419 citations. Iterative review yielded 84 unique studies (Figure E1). We focused our analysis on prospective studies with explicit (i.e., reproducible) diagnostic methods. Using these criteria, 31 studies were identified (Table E4). Agreement between abstractors on study

selection was near perfect, with a kappa statistic of 0.91 (38).

The 31 studies (3,905 patients) had a median sample size of 43 (interquartile range [IQR], 25–85). Twenty-eight studies were either observational or case series, and three were randomized trials (Table 4). Twenty-six studies (84%) specifically enrolled patients for the clinical assessment of weakness, with 25 studies (80%) excluding patients with other diagnoses causing weakness. The majority of studies did not have, or did not report, the use of protocolized sedation (96%) or ventilator weaning (88%), which could affect the time to cooperation with a cooperative physical examination. Most studies reported outcomes at ICU (23%) and hospital (55%) discharge. Only six studies (19%) reported any outcome measure (e.g., weakness, quality of life) beyond hospital discharge. The most common reasons for

admission to the ICU were respiratory failure (39%) and sepsis (15%). Patients with ICUAW had a median age of 61 (IQR, 53–65) years and a median Acute Physiology and Chronic Health Evaluation II score of 20 (IQR, 18–21).

Question 1: In Which Critically Ill Patient Groups Does ICUAW Occur with a Clinically Significantly Increased Frequency?

It has been hypothesized that severe sepsis, difficulty weaning from mechanical ventilation, and prolonged mechanical ventilation are associated with ICUAW. Eleven studies reported data about the prevalence of ICUAW among these populations (Table E5) (7, 8, 17, 39–49). Two of the studies were excluded from our analysis because they lacked a control group (39, 40).

A pooled analysis from seven studies recruiting patients with severe sepsis (262 patients; median, 43; IQR, 28–56) (17, 41, 42, 44–47) indicated that the incidence of significant weakness was significantly higher than that observed in studies of other patient groups (5 studies, 504 patients; median, 95; IQR, 50–136) (64 vs. 30%, $P < 0.001$) (7, 8, 43, 48, 49). However, in four prospective studies (7, 8, 48, 49), the prevalence of sepsis at any time during their presentation was no different whether they developed weakness or not (52% in weak patients vs. 56% of those without weakness, $P = 0.46$). Seven studies found that the duration of mechanical ventilation was longer among patients diagnosed with ICUAW than among patients without ICUAW (median, 25 d [IQR, 12–33 d] vs. 18 d [IQR, 8–18.5 d]; $P = 0.06$) (7, 8, 17, 41, 47–49). This has been confirmed in more recent studies (50). Pooled analysis of 14 studies that enrolled patients after a specific period of mechanical ventilation suggests that the longer the exposure to mechanical ventilation the higher the incidence of ICUAW (33% in studies enrolling patient on ventilation ≤ 5 d vs. 43% in those enrolled after ≥ 7 d, $P = 0.01$) (7, 8, 17, 25, 41, 48, 49, 51–57).

Question 2: What Tests Are Used to Identify ICUAW and How Are They Applied in Critically Ill Patients?

In our systematic review, the most common diagnostic tests for ICUAW were physical examination (84% of studies), EMG (90%

Table 3. Clinical Questions

Clinical questions used in the deliberations of how to make the diagnosis of ICU-acquired weakness
In which critically ill patient groups does ICUAW occur with a significantly increased frequency?
What tests are used to identify ICUAW and how are they applied in critically ill patients?
How is electrophysiological testing used in critically ill patients when making the diagnosis of ICUAW?
What is the recommended practical approach to identifying critically ill patients who develop ICUAW?

Definition of abbreviation: ICUAW = intensive care unit-acquired weakness.

Table 4. Study Characteristics

Characteristic	Studies (N = 31)
No. patients evaluated for ICUAW	
Total	3,095
Patients with ICUAW, no. (%)	1,019 (33)
Per study, median (IQR)	43 (25–75)
Study design, no. (%)	
Prospective cohort study	28 (90)
Randomized controlled trial	3 (10)
Patient enrollment criteria, no. (%)*	
Mechanical ventilation	12 (39)
Failure to wean from mechanical ventilation	2 (6)
SIRS/sepsis and/or multiorgan failure	10 (32)
ALI/ARDS	1 (3)
Clinical assessment of weakness	26 (84)
Other	5 (16)
Exclusion of alternative diagnoses for ICUAW, no. (%)	
Yes	25 (80)
No	3 (10)
Unclear/not reported	3 (10)
Duration of follow-up, no. (%)	
ICU	9 (29)
Hospital	16 (52)
Posthospital discharge	6 (19)

Definition of abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ICUAW = intensive care unit–acquired weakness; IQR = interquartile range; SIRS = systemic inflammatory response syndrome.

*Included studies could have enrolled patients with more than one criterion.

of studies), and nerve conduction studies (NCS) (84% of studies) (Table 5). None of the studies compared two diagnostic approaches; rather, most used the tests sequentially if abnormalities were identified on initial testing.

Twenty-six studies (2,318 patients) evaluated physical examination with MMT to diagnose ICUAW (Table E6) (7, 8, 39, 40, 42–45, 47–49, 51–66). Thirteen of those studies (887 patients) (7, 8, 39, 43, 44, 48, 53, 54, 56, 57, 64–66) used a composite MRC (Table E7) score to define strength. Nine of the studies (669 patients) clearly stated an MRC score threshold to define significant weakness (Table E8) (7, 8, 43, 48, 53, 54, 56, 57, 64). Seven of these studies (494 patients) used less than 80% of

the maximum score as the threshold to diagnose ICUAW (7, 8, 43, 48, 56, 57, 64). Only four studies (7, 8, 43, 53) quantified cooperation before the performance of MMT.

MMT was correlated with EMG/NCS in 12 studies (8, 42, 44, 45, 47, 52, 54, 56, 57, 60, 65, 66). In the aggregate (214 patients), these studies demonstrated that 80% of subjects with abnormal EMG/NCS studies had moderate to severe weakness (varied thresholds). The frequency of clinical weakness did not vary based on the threshold MRC used (77% in MRC threshold vs. 84% in other definitions of weakness, $P = 0.2$). The frequency of EMG abnormalities (>95%) did not vary with use of MRC (four studies

Table 5. Diagnostic Methods for Intensive Care Unit–acquired Weakness

Diagnostic Method	Studies (N = 31)
Physical examination	26 (84)
EMG	28 (90)
Nerve conduction studies	26 (84)
Direct muscle stimulation	6 (19)
Muscle biopsy	8 (26)
Nerve biopsy	2 (6)

Data are presented as n (%).

[108 patients]) or other subjective strength scales (eight studies [228 patients]). One study directly compared initial EMG/NCS findings in the ICU with the final clinical diagnosis with MMT. This study showed that the positive predictive value of in ICU EMG for the final diagnosis of weakness was 50%, and its negative predictive value was 89% (57). Other diagnostic studies like muscle or nerve biopsy were used too infrequently to warrant comment.

Question 3: How Is Electrophysiological Testing Used in Critically Ill Patients When Making the Diagnosis of ICUAW?

Use of electrophysiological testing in clinical practice is variable. In our review, 28 (2,248 patients) and 26 (1,813 patients) studies used EMG and NCS, respectively. The 15 studies that evaluated EMG and/or NCS criteria for ICUAW found varying diagnostic thresholds (Table E9) (8, 17, 25, 39, 41, 44, 48, 49, 55, 56, 58, 59, 65–67). Moreover, five studies (191 patients) that evaluated direct muscle stimulation reported variability in the muscles tested and the threshold used for the diagnosis of ICUAW (39, 56, 59, 65, 66). Studies of EMG or NCS in uncooperative patients tended to perform the tests early during their ICU stay (e.g., Day 2–10), whereas studies in cooperative patients with abnormal MMT tended to perform them only if the abnormalities persisted (e.g., 2–7 d).

Rationale for Diagnosis

Physical and occupational therapist intervention to encourage ambulation reduces the duration of delirium (23), increases ventilator-free days (23), and improves functional status (21), 6-minute-walk distance, and subjective feeling of well-being (20) at hospital discharge in heterogeneous populations of ICU patients. Despite the benefits of physical rehabilitation, it may not be feasible to provide it to all ICU patients. An alternative approach is to provide physical rehabilitation to subtypes of ICU patients who are most likely to benefit (68–70). Patients with ICUAW may be such a group.

The possibility that patients who develop ICUAW might benefit from physical therapy is suggested by two case series. In the first series of 35 patients with ICUAW who received only infrequent physical therapy when deemed necessary

by a treating physician, four patients were able to be discharged home (11%) after their critical illness. Of the remaining 31 patients, 11 (31%) died and 20 (57%) were discharged to a rehabilitative or long-term medical facility (7). In contrast, the second series followed 19 patients with ICUAW who all underwent physical therapy for an average of 30 minutes a day for 5 days a week until discharge and found that 6 patients were able to be discharged home (32%) after their critical illness. Of the remaining 13 patients, 2 (11%) died and 11 (57%) were discharged to a rehabilitative or long-term medical facility (24). The severity of illness was similar in the case series (a Sequential Organ Failure Assessment score of 8 [7] and 6 [24]). Taken together, the case series suggest that physical rehabilitation might be associated with increased probability of discharge to home instead of another facility (relative risk, 2.76), although there were too few events to definitively confirm or exclude an effect (95% confidence interval, 0.88–8.60).

Such evidence is very low quality (Table E3), meaning that the committee has very little confidence in the estimated effect. The very low quality of the evidence reflects that the estimates were derived from case series, comparisons were across series rather than within series, and there were few patients and events. Given the very low-quality evidence that making a diagnosis of ICUAW improves clinical outcomes, the guideline development committee recommends performing well-designed and -executed randomized trials that measure and properly report clinical outcomes of physical rehabilitation in patients with ICUAW. This includes research that improves our understanding of the role of patient factors and comorbidities in the likelihood of developing ICUAW and the response to treatment. Furthermore, the influence of this diagnosis on patient preferences and their perception of how it affects their medical decision making should be determined through future research. The committee is certain that additional research is necessary to prove whether physical therapy improves outcomes in patients with ICUAW, and such evidence is necessary before deciding whether or not routine diagnostic testing for ICUAW is indicated. This should be seen as distinct from the issue of the value of physical rehabilitation in general populations of mechanically

ventilated critically ill patients that has a more direct body of evidence (20, 21, 71) and is not specifically addressed in this document.

Even though the evidence that making a diagnosis of ICUAW improves clinical outcomes is very low, many members of guideline development committee routinely test high-risk ICU patients for ICUAW (i.e., patients with severe sepsis, difficulty being liberated from mechanical ventilation, or receiving prolonged mechanical ventilation). The approach is based on unsystematic clinical observations that making a diagnosis of ICUAW may have beneficial effects that are seldom measured, including the prevention of unnecessary testing for alternative diagnoses (28), earlier initiation of physical and occupational therapy, and increased accuracy of counseling about the anticipated duration of mechanical ventilation, rehabilitative services, and physical recovery after critical illness (11, 19, 23, 29–31). Moreover, the members of the guideline development committee who perform routine diagnostic testing argue that the potential, albeit unproven, benefit of early physical and occupational therapy is sufficient to warrant diagnostic testing, because therapy can be performed without harm to the patient and with minimal burden to providers. In the case series that followed patients with ICUAW who received physical therapy, there were no adverse events reported (24); in two randomized trials of physical therapy in a heterogeneous ICU population, there was only one adverse event reported among 194 patients and more than 600 physical therapy sessions (20, 21). This was confirmed in a more recent systematic review (72). MMT is performed in cooperative patients and electrophysiological testing in uncooperative patients.

Discussion

The committee used state-of-the-art guideline methodology to generate clinical questions, identify and appraise relevant evidence, and consider whether routine diagnostic testing for ICUAW is warranted. The process yielded a clear understanding of current gaps in the available literature, most notably the paucity of evidence that physical rehabilitation (or any alternative therapy) improves clinical outcomes in

patients diagnosed with ICUAW. By generating objective evidence that clinical outcomes can be improved, aggressive efforts aimed to diagnose patients with ICUAW can be justified.

Despite this lack of current evidence, there are several reasons that many members of the guideline development committee perform routine diagnostic testing to identify patients with ICUAW in their clinical practices. First, ICUAW is associated with worse clinical outcomes, and nonrecognition could lead to inappropriate expectations of recovery. Second, many believe that the potential, albeit unproven, benefits of physical therapy outweigh the downsides, because therapy can be performed without harm to the patient and with minimal burden to providers. Third, patients with ICUAW appear at risk for recurrent respiratory failure and nosocomial pneumonia (7, 17) possibly related to reduced neuromuscular reserve (15, 16). Respiratory therapists or others could focus on respiratory support and pulmonary airway clearance in patients with ICUAW to minimize these risks. Finally, a clear phenotypic description of these patients could facilitate further research to explore causes and interventions.

Although there are important reasons to diagnose ICUAW, there are also several limitations to our approach that were discussed during the committee's deliberations. The limitations include our lack of understanding of how to interrupt the pathophysiology that leads to ICUAW, the heterogeneity of critically ill populations, and limitations inherent to the tools available. Finally, the reduced quality of life and poor functional independence of critically ill patients after critical illness needs further research to define the impact of reduced strength on this outcome.

Lack of Understanding of Mechanisms

There has been significant work focused on the cellular alterations in specific causes of ICUAW (32, 73–75); however, such efforts have not resulted in specific pharmacologic interventions. As a result, the advantages of diagnosing ICUAW are less than if one existed. An area that has received considerable attention is the effects of immobility (73, 76), which has led to the promotion of sedative interruption and early rehabilitation therapy in a variety of settings (20, 21, 76–81). However, even these interventions

are limited by an incomplete understanding of the pathophysiology and delayed recognition (82). Additionally, as we learn more about the link between critical illness and persistent physical limitation (83), we must dissect what aspects of critical illness (immobility, inflammation, lack of exercise, cognitive deficits) lead to disability (82, 84).

Heterogeneity of Critically Ill Populations

Heterogeneity of critically ill populations is another important barrier, particularly as it pertains to functional recovery, as this is a major concern among patients recovering from critical illness (18, 19, 85). For instance, functional outcomes among survivors of acute respiratory distress syndrome (ARDS) can vary based on age and chronic underlying comorbidity (11, 86, 87). This occurs despite similar severity and duration of illness. Younger, previously employed patients with ARDS without comorbidity have improved survival and return to independence when compared with the elderly (9, 85, 88). Recovery may vary because the syndrome has heterogeneous underlying pathology or treatment has influenced the muscles' response to injury (89). Understanding this variability may allow diagnostic efforts to target patients most likely to benefit from diagnosis.

Limitations of Diagnostic Tools

The diagnostic tests used to identify ICUAW are limited by reproducibility, the narrow window during which they can be applied, and the lack of a universally accepted and validated "gold standard." Volitional testing (e.g., MMT), although reliable in cooperative

patients (90), is inherently challenging given the available scales (91) and bias introduced by detection after awakening (91). Despite these limitations, a more reliable test has not emerged.

Relation between Functional Dependence and Acquired Weakness

By defining the long-term impact of critical illness on patients returning to society, the attention paid to developing interventions is likely warranted. The link between ICUAW/muscle strength and physical function (strength, timed walk distance, etc.) and patient-reported quality of life measures has been clearly reported (83). However, given the simultaneous evolution in our understanding of cognitive (92), psychiatric (93), and physical impacts of critical illness, a better understanding of the signal of functional independence is needed to understand how to target physical recovery. This is important as, in the aggregate, functional independence is more readily monitored than any more specific symptom and thus likely to remain a pragmatic target of intervention. Current studies of combined interventions targeting both physical and cognitive performance may be the only way for us to tease apart the relative contribution of each of these domains (71). This understanding would have direct policy implications and would assist clinicians and patients in prioritizing future recommended interventions.

Finally, we have emphasized the assessment of strength in this document as a primary modality of identifying these patients. This was done due to the universal

availability of tests of muscle strength; however, electrophysiology has aided our understanding of this syndrome similar to other diseases like the Guillain-Barré syndrome (94). It is possible that electrophysiology may aid in determining a patient's ability to respond to certain interventions. If this proves true, we should alter the assumption that electrophysiology should be secondary to physical signs of weakness in any diagnostic approach.

In the absence of clarity regarding the issues outlined above, we are unable to explicitly advocate for a systematic approach to identifying patients with ICUAW. In this case, ICU clinicians can only leverage the currently available evidence for the application of early rehabilitation in a broad group of critically ill patients to prevent or ameliorate physical disability. Although these data are significant, some institutions may not be adequately resourced to deliver this comprehensive approach.

This process can and should be revised once more rigorous studies on intervention in ICUAW and comparisons of diagnostic testing have been completed and more clinical data are available. Our document is intended to advance both the clinical and research agendas for ICU practitioners. Standard case identification can quantify the problem of ICUAW and focus existing limited rehabilitative or other resources on these patients (77); however, true benefit needs to be proven first. Until then, we hope this document serves to illustrate what has been learned from the diagnostic strategies used to date and helps promote a better understanding of the clinical problems faced in discussing this complex syndrome. ■

This guideline was prepared by an *ad hoc* subcommittee of the Assembly on Critical Care and the Assembly on Nursing.

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