AMERICAN THORACIC SOCIETY DOCUMENTS

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

Contents

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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
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)	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.	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.

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).

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.

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 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 [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.

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 (%).

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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Review Article

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The incidence of intensive care unit-acquired weakness syndromes: A systematic review

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Abstract

We conducted a literature review of the intensive care unit-acquired weakness syndromes (critical illness polyneuropathy, critical illness myopathy and critical illness neuromyopathy) with the primary objective of determining their incidence as a combined group. Studies were identified through MEDLINE, Embase, Cochrane Database and article reference list searches and were included if they evaluated the incidence of one or more of these conditions in an adult intensive care unit population. The incidence of an intensive care unit-acquired weakness syndrome in the included studies was 40% (1080/2686 patients, 95% confidence interval 38–42%). The intensive care unit populations included were heterogeneous though largely included patients receiving mechanical ventilation for seven or more days. Additional prespecified outcomes identified that the incidence of intensive care unit-acquired weakness varied with the diagnostic technique used, being lower with clinical (413/1276, 32%, 95% CI 30–35%) compared to electrophysiological techniques (749/1591, 47%, 95% CI 45–50%). Approximately a quarter of patients were not able to comply with clinical evaluation and this may be responsible for potential underreporting of this condition.

Keywords

Critical care, intensive care, epidemiology, muscle weakness, intensive care unit-acquired weakness

Introduction

Worldwide, the majority (70–80%) of patients admitted to an intensive care unit (ICU) now survive;[1–5] follow-up has identified multiple sequelae with generalised weakness in particular found to be a common and troublesome problem.[6–9] Whilst there has been major heterogeneity in terminology used to label this generalised weakness, a critical illness associated polyneuropathy, myopathy and neuromyopathy (where both neuropathy and myopathy coexist) have broadly been identified. These syndromes are now all included under the clinical diagnostic label of intensive care unit-acquired weakness (ICUAW).[10]

The development of an ICUAW syndrome may have important consequences on patient outcomes; prolonged ventilatory weaning,[11,12] increased ICU[12] and hospital length of stay,[13] increased hospital mortality,[14,15] increased 180-day mortality[16] and persistent disabling weakness with reduced quality of life out to one year from ICU discharge.[17–19] There may also be a number of potentially modifiable risk factors for ICUAW; prolonged ICU stay/bed rest,[20,21] hyperglycaemia/insulin therapy,[13,22–24] corticosteroids[20] and neuromuscular blockers.[14]

Unfortunately, there is marked heterogeneity across the studies of ICUAW. A systematic review by Stevens et al.[13] highlighted, for example, the heterogeneity in the diagnostic criteria used. This currently makes drawing firm conclusions regarding ICUAW difficult and may partly explain some of the inconsistent findings across the studies, such as an incidence varying from 9%[25] to 86%.[26]

With the increasing recognition that the ICU care we deliver needs to ensure the optimal functional outcome of patients, further study and a better understanding of ICUAW are important next steps. There have been a significant number of studies published[8,15,16,23,24,27–32] since the previous systematic

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review supporting updating the estimate of the incidence of ICUAW. In addition, with the marked variation in diagnostic criteria used across studies, further investigation of this heterogeneity may be useful in identifying trends, for example in incidence, within the diagnosis. This may then allow more homogenous groups and their outcomes to be identified for intervention and prognostication.

Unfortunately, the inconsistent reporting of the diagnostic criteria precludes its influence on incidence from being evaluated directly. However, part of the heterogeneity within the diagnostic criteria may relate to the varying diagnostic techniques used – clinical, neurophysiological or histological examination. The diagnostic techniques used across the studies are adequately reported and could be used to identify any variation in the incidence of ICUAW according to the diagnostic technique used.

The aims of this review are: (1) to determine the approximate incidence of all the ICUAW syndromes as a group, (2) to determine the incidence of the ICUAW syndromes categorised by diagnostic technique (clinical, electrophysiological and histological diagnoses) and (3) to determine the incidence of failure of completion of diagnostic assessment and the attributable causes (that are not a lack of study consent) categorised by diagnostic technique.

Methods

Data sources and searches

The online databases MEDLINE, Embase and the Cochrane databases were searched from the period 1977 until 1 July 2011 to identify studies to include in this review. The search terms used were: muscle weakness, paresis, polyneuropath(y)/(ies), muscle hypotonia, muscular disease(s), intensive care unit(s), intensive care, critical care, critical illness, respiration artificial, artificial ventilation. These terms were mapped to the appropriate subject headings and 'exploded'. The search was limited to studies published in English and those involving humans.

The title and abstract of all publications identified by the search strategy were screened, with the full text of all those describing an ICUAW syndrome reviewed. The reference list of each full text article reviewed was screened to identify additional relevant papers.

Study selection

Studies fulfilling the following eligibility criteria were included: (1) patients were admitted to an adult ICU, (2) patients were diagnosed with an ICUAW (critical illness polyneuropathy, critical illness myopathy or critical illness neuromyopathy), (3) sufficient data to calculate the incidence of an ICUAW was provided, (4) study patients were not potentially included in another study included in this review and (5) the full-length report was published. Patients with weakness attributed to a specific aetiology (e.g. spinal cord compression) were excluded.

Studies where the diagnostic criteria were either not consistent with a diagnosis of an ICUAW or were inadequate were excluded. Whilst there has recently been consensus diagnostic criteria published,[10] all studies included in this review recruited patients prior to this publication where diagnostic criteria were variable. The minimum criteria required for study inclusion were any of the following: (1) a new clinical diagnosis of generalised weakness determined by an objective clinical assessment tool (e.g. Medical Research Centre sum scores), (2) reduced compound motor and sensory nerve action potential amplitudes consistent with critical illness polyneuropathy, (3) normal sensory nerve action potential amplitudes with either of short duration, low amplitude motor potentials on electromyography (EMG) or low-amplitude motor potentials and nerve:muscle ratio >0.5 on direct muscle stimulation consistent with critical illness myopathy, (4) muscle histology consistent with critical illness myopathy or (5) a combination of neurophysiological abnormalities as given above consistent with critical illness neuromyopathy.

For the third question of this review addressing the incidence of failure to complete diagnostic testing, only papers presenting this information were included in this part of the analysis. The denominators abstracted from each paper for these calculations were the number of patients analysed in the study plus the number who were not included because of failure to complete the diagnostic evaluation.

Data extraction and quality assessment

A modified version of the validated Newcastle–Ottawa Scale (NOS)[33] with the addition of three further criteria suggested by Altman et al.[34] was used to appraise the observational studies. The NOS evaluates three domains; the selection of the study populations (range 0–4 points), the comparability of the study populations (range 0–2 points) and the assessment of the outcomes (range 0–3 points). The modified NOS we used had three additional assessments (objectivity of diagnostic criteria used (0–1 point), appropriateness of diagnostic criteria (0–1 point) and ability of diagnostic criteria to differentiate critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness neuromyopathy (CINM) (range 0–2 points) within the outcome domain (range 0–7 points). The modified scale has a maximum score of 13 with a score of 0–4 being judged as a low-quality, 5–8 as medium-quality and 9–13 as a high-quality study. The modified NOS was agreed by the authors prior to commencing the review.

Randomised controlled trials (RCTs) were appraised according to the Cochrane Collaboration's assessment tool for risk of bias.[35] Each study was assessed by one of the authors for quality using these tools.

Data synthesis and analysis

Patient, illness, treatment and study design data were abstracted using a standardised data collection sheet and collated in Excel (Microsoft Corporation Redmond, WA, USA). Professional statistical advice was obtained and confidence interval (CI) analysis (95% CIs) on proportions using aggregated original study data was performed by one of the study authors using Confidence Interval Analysis Version 2.2.0 (University of Southampton, UK, 2000–2011).

Results

Study search and selection

The results of the literature search are shown in Figure 1; 33 studies including 2686 patients were evaluated in this review. The characteristics of the included studies are shown in Table 1. Of the 33 studies, 27 were prospective cohort studies, two were

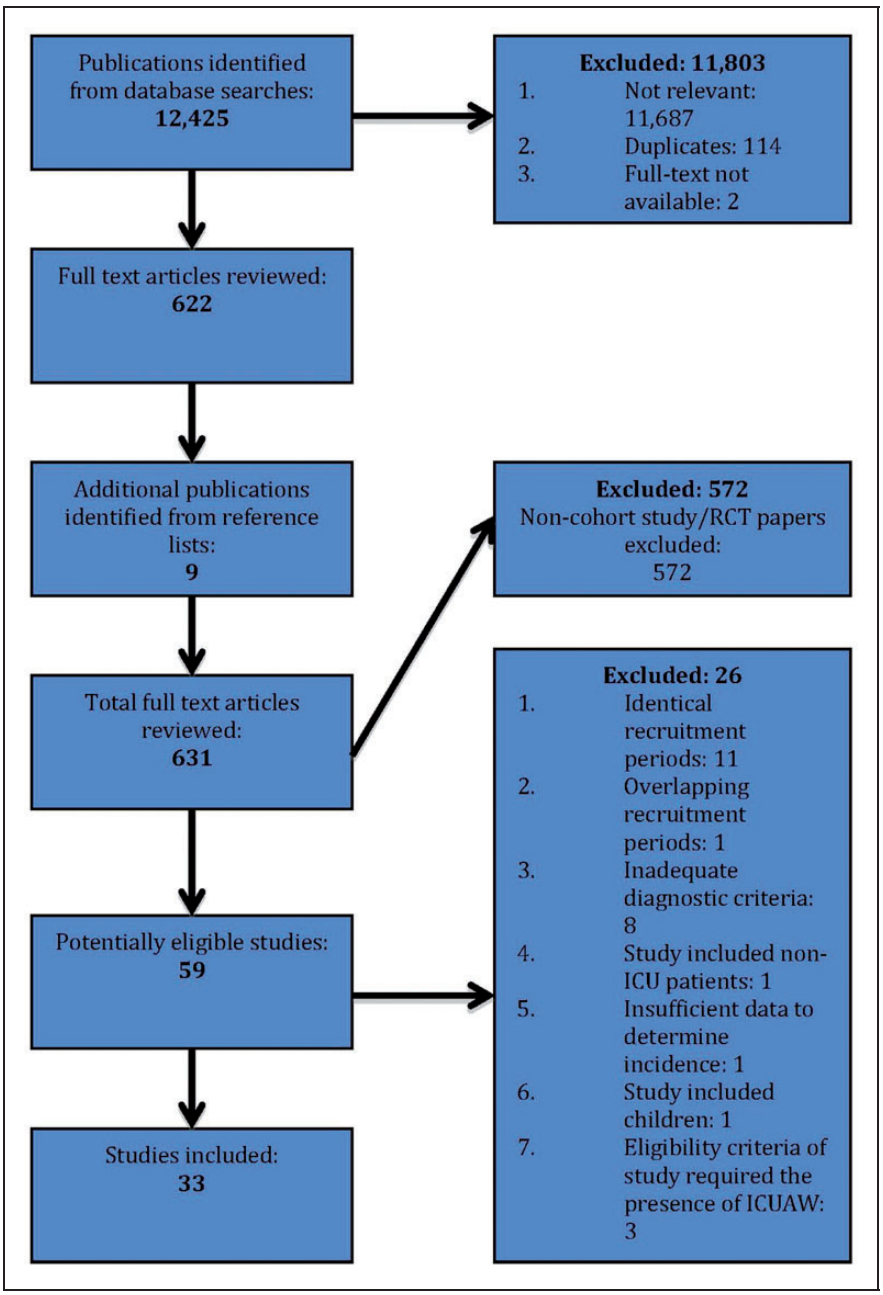

Figure 1. Literature search results.

Table 1. Study characteristics.

References	Study design, eligibility and study period	ICU population
Ahlbeck et al.[36]	Prospective cohort study Mechanical ventilation for three days Study period not stated	ICUs in a single University hospital in Sweden Mixture of medical, surgical, trauma and neuro-surgical admission diagnoses Age (mean): 54 (range 21–79) years Males: 7 (70%)
Ali et al.[28]	Prospective cohort study Mechanical ventilation >5 days ICU admission between May 2005 and April 2007	Five medical ICUs in USA Range of medical admission diagnoses and comorbid conditions Age (mean): 58 (*SD* 16) years Males: 48%
Amaya-Villar et al.[43]	Prospective cohort study Acute exacerbation of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation for > 48 h and receiving ⩾240 mg methylprednisolone in the first 48 h ICU admission between 1997 and 2000	Single Spanish ICU Solely COPD patients evaluated Age (mean): ICUAW 62 (*SD* 9) years, no-ICUAW 66 (*SD* 7) years
Bednarik et al.[51]	Prospective cohort study ⩾2 organ failures and within 24 h of onset of critical illness Meeting study entry criteria between January 2000 and November 2002	One general and one neurological ICU in a single hospital in the Czech Republic Admission diagnoses provided incomplete; mixture of neurological and medical/surgical admission diagnoses in those provided Age (range): 22–81 years
Bercker et al.[37]	Retrospective cohort study Consecutive acute respiratory distress syndrome (ARDS) patients ICU admission between May 1998 and November 2001	Single tertiary ARDS ICU in Germany Solely ARDS patients Age (median): 37 (IQR 21–56) years
Berek et al.[38]	Prospective cohort study systemic inflammatory response syndrome (SIRS)/sepsis with multiorgan failure Study period: September 1992–August 1993	ICUs not described ICU admission diagnosis was predominately polytrauma with some additional general surgical diagnoses Age (median): 56 (range 23–77) years Males: 17/22 (77%)
Brunello et al.[16]	Prospective cohort study Mechanical ventilation ⩾48 h and ⩾2 SIRS criteria Study period: September 2005–May 2006	ICUs not described ICU admission diagnoses were predominately a mix of medical and surgical (general and cardiac) with a small number of trauma diagnoses Age (mean): 67 (*SD* 14) years Males: 28/39 (72%)
Campellone et al.[25]	Prospective cohort study Patients undergoing orthotopic liver transplant (OLTx) and either ventilated for >7 days or hospitalised >14 days Study period: August 1995–February 1996	Single ICU in USA Solely adult patients undergoing OLTx Age (mean): 53 (range 17–73) years
Coakley et al.[44]	Prospective cohort study ICU stay ⩾7 days and ⩾1 organ failing 11-month study period, time period not stated	Single ICU in UK Admission diagnoses a mixture of medical, surgical and trauma Age (range): 20–72 years Males: 15/23 (65%)
Coakley et al.[39]	Prospective cohort study ICU stay ⩾7 days 3-year study period, time period not stated	Single ICU in UK Admission diagnoses a mixture of medical, surgical (general and cardiac) and trauma Age (range): 27–84 years Males: 23/44 (52%)
De Jonghe et al.[20]	Prospective cohort study Mechanical ventilation for ⩾7 days Study period: began March 1999 for mean duration 8.6 months	Three medical and two surgical ICUs in four hospitals in France Admission diagnoses a mixture of medical, surgical and trauma Age (mean): 62 (*SD* 15) years Males: 69/95 (73%)

(continued)

Table 1. Continued.

References	Study design, eligibility and study period	ICU population
De Letter et al.[45]	Prospective cohort study Mechanical ventilation for ⩾4 days Study period: May 1994–July 1996	Single ICU in Holland Admission diagnoses not provided Age (median): 70 (range 15–85) years Males: 55/98 (56%)
Douglas et al.[40]	Prospective cohort study Mechanical ventilation for severe asthma 18-month study period, no further information provided	Single ICU in Australia Solely patients with asthma Age (mean): 39 (*SD* 17) years Male: 5/25 (20%)
Druschky et al.[41]	Prospective cohort study Mechanical ventilation for >4 days Study period: April 1997–December 1998	Single neurological ICU in Germany Admission diagnoses were either ischaemic stroke or intracerebral haemorrhage Age (mean): ICUAW 64 (*SD* 8) years, non-ICUAW 70 (*SD* 8) years Males: 18/28 (64%)
Garnacho-Montero et al.[14]	Prospective cohort study Sepsis with multiorgan failure and ventilated for >10 days Study period: November 1996–March 1999	Single mixed medical/surgical ICU in Spain Primary diagnoses were predominately abdominal and chest sepsis with small numbers of other sources of sepsis Age (mean): ICUAW 62 (*SD* 14) years, no ICUAW 62 (*SD* 12) years
Garnacho-Montero et al.[12]	Prospective cohort study Severe sepsis/septic shock requiring mechanical ventilation ⩾7 days Study period: July 1999–December 2002	Single mixed medical/surgical ICU in Spain Primary diagnoses were predominately abdominal and chest sepsis with small numbers of other sources of sepsis Age (mean): ICUAW 61 (*SD* 15) years, no ICUAW 62 (13) years Males: 39/64 (61%)
Hermans et al.[23]	Randomised controlled trial, preplanned subgroup analysis Eligibility not stated Study period: March 2002–May 2005	Single medical ICU in Belgium Preplanned subanalysis of intensive insulin therapy (IIT) vs. conventional insulin therapy (CIT) in those staying ⩾7 days Range of medical admission diagnoses Age (mean): CIT 64 (*SD* 16) years, IIT 61 (*SD* 15) years Males: 253/420 (60%)
Hough et al.[32]	Prospective cohort study Three days mechanical ventilation Study period: four months in 2006 and 2007	ICUs in a single hospital in USA. Mixture of surgical, medical and neurological admissions Age (mean): 49 (*SD* 15) years Males: 71%
Hund et al.[46]	Prospective cohort study Sepsis and prolonged mechanical ventilation Study period not stated	Single surgical ICU in Germany Mixture of general, cardiac, neurological and trauma surgical patients Age (median): 70 (range 16–80) years Males: 19/28 (68%)
Kesler et al.[29]	Retrospective cohort study Acute severe asthma requiring mechanical ventilation Study period: May 1983–May 1995 and May 1995–May 2004	Single medical ICU in USA Solely patients presenting with acute severe asthma Age (mean): Pre-1995 cohort 39 (*SD* 17) years, post-1995 cohort 38 (*SD* 13) years Males: Pre-1995 56%, post-1995 45%
Khan et al.[47]	Prospective cohort study Severe sepsis diagnosed within 72 h of ICU admission and 10 days of hospital admission and an ICU stay ⩾7 days Study period: April 2003–December 2004	Two medical ICUs in two hospitals in USA Approximately 50% chest source of sepsis, no further information provided Age (mean): ICUAW 53 (*SD* 16) years, no ICUAW 46 (*SD* 16) years Males: not stated

(continued)

Table 1. Continued.

References	Study design, eligibility and study period	ICU population
Latronico et al.[27]	Prospective cohort study ICU admission and a Simplified Acute Physiology II Score between 35 and 70 Study period: January 1998–March 2001	Nine ICUs in Italy Mixture of medical, surgical (general and neurological) and trauma admission diagnoses Age (median): 50 (range 18–85) years Males: 63/92 (69%)
Leijten et al.[48]	Prospective cohort study Mechanical ventilation >7 days Study period: July 1991–January 1993	Single mixed medical and surgical ICU in Holland Admission diagnoses were a mixture of surgical (general, thoracic and neurological), medical and trauma Age (mean): ICUAW 59 (*SD* 14) years, no ICUAW 55 (*SD* 17) years Males: 26/38 (68%)
Mohr et al.[49]	Prospective cohort study ICU patients with multiorgan failure 2-year study period, time period not stated	Single mixed surgical (general and neurological) and trauma ICU in Germany Primary diagnosis predominately trauma with smaller numbers of surgical (general and neurological) and medical diagnoses Age (median): no sepsis/no ICUAW 45 (range 16–69) years, sepsis/no ICUAW 52 (range 21–76) years, sepsis/ICUAW 48 (range 20–71) years Males: 19/33 (58%)
Nanas et al.[24]	Prospective cohort study ICU stay >10 days Study period: August 2005–September 2006	Single mixed medical and surgical ICU in Greece Mixture of medical, surgical and trauma admission diagnoses Age (mean): 54 (*SD* 19 years) Males: 127/185 (69%)
Routsi et al.[31]	Randomised controlled trial ICU patients with an admission Acute Physiology and Chronic Health Evaluation II score ⩾13 Study period: September 2007–June 2009	Single mixed medical and surgical ICU in Greece Randomised controlled trial of electrical muscle stimulation (EMS) to lower limbs versus usual care Mixture of medical, surgical and trauma admission diagnoses Age (mean): EMS group 55 (range 23–82) years, control 59 (range 19–84) years Males: EMS group 19/24 (79%), control 22/28 (79%)
Schweikert et al.[8]	Randomised controlled trial (RCT) Mechanical ventilation for <72 h and predicted to require a further 24+ h of mechanical ventilation Independent at baseline Study period: June 2005–October 2007	Two medical ICUs in USA RCT of early physical and occupational therapy versus usual care Mixture of medical admission diagnoses Age (median): intervention group 58 (IQR 36–69) years, control group 54 (IQR 47–66) years Males: 52/104 (50%)
Sharshar et al.[15]	Prospective cohort study Mechanical ventilation for ⩾7 days Study period: June 2003–June 2005	Two medical, one surgical and one mixed medical/surgical ICU in three hospitals in France Approximately 70% had a medical admission diagnosis Age (median): 65 (IQR 52–77) years Males: 75/115 (65%)
Tepper et al.[26]	Prospective cohort study Septic shock Study period: January 1995–August 1995	Single ICU in Holland Predominately chest and abdominal sources of sepsis with small numbers of other sources Age (mean): 57 (range 25–79) years Males: 18/25 (72%)

(continued)

Table 1. Continued.

References	Study design, eligibility and study period	ICU population
Thiele et al.[50]	Prospective cohort study Open heart surgery and mechanical ventilation >3–5 days Study period: June 1997–September 1998	Single cardiac surgical ICU in Germany Predominately bypass graft surgery with small numbers of valve surgery Age (mean): ICUAW group 66 (*SD* 5) years, non-ICUAW 68 (*SD* 7) years Males: 13/19 (68%)
Van den Berghe et al.[22]	Randomised controlled trial, preplanned sub-group analysis Adult patients in ICU for ⩾7 days Study period not stated	Single surgical ICU in Belgium RCT of conventional (CIT) vs. intensive insulin therapy (IIT) Mixture of cardiac, thoracic, general, vascular, neurological, trauma and transplant surgery admission diagnoses Age (mean): CIT 61 (*SD* 16) years, IIT 61 (*SD* 15) years Males: CIT 69%, IIT 67%
Weber-Carstens et al.[30]	Prospective cohort study Mechanically ventilated patients with a Simplified Acute Physiology II Score ⩾20 on three consecutive days within first seven days of ICU admission 18-month study period, time period not stated (dmCMAP: direct muscle compound motor action potential)	Single surgical ICU in Germany Mixture of trauma, pneumonia and abdominal sepsis as the predominate admission diagnoses Age (median): normal dmCMAP 42 (IQR 26–59) years, abnormal dmCMAP 53 (*SD* 40–61) years Males: 28/56 (50%) (only data provided)
Witt et al.[42]	Prospective cohort study Sepsis with multiple organ failure and ICU stay >5 days 14-month study period, time period not stated	Single hospital in Canada, single mixed ICU Mixture of medical, surgical (cardiac, general, vascular, gynaecological and thoracic) and trauma admission diagnoses Age (mean): 64 (range 21–78) years Males: 22/43 (51%)

Note: ICUAW, intensive care unit-acquired weakness; *SD*, standard deviation; IQR, inter-quartile range.

retrospective cohort studies and four were randomised controlled trials.

Quality of included studies

Eleven out of the 29 (38%)[25,28,29,32,36–42] observational studies were graded of low quality, 17 out of 29 (59%)[12,14–16,20,24,26,27,30,43–50] as medium and one (3%)[51] as high quality. There were four RCTs included; two studies were deemed of low risk,[22,23] one unclear risk[8] and one with high risk[31] of bias.

Incidence of ICUAW

The 33 studies included 2686 patients with 1080 (40%, 95% CI 38–42%) patients meeting the criteria for an ICUAW (see Table 2). The median incidence of an ICUAW across the studies was 47% (range 9–86%).

Incidence of ICUAW by diagnostic technique

Fifteen studies including 1276 patients made the diagnosis of an ICUAW using clinical examination, 20 studies including 1591 patients used electrophysiological examination to make the diagnosis and a single study of 23 patients used histological assessment (see Table 3). The incidence of ICUAW syndromes in the subgroups of patients separated by diagnostic technique is given in Table 3.

Failure of completion of diagnostic assessment

Fourteen studies including 1488 patients using clinical assessment and 17 studies including 742 patients using neurophysiological assessment provided data on failure of completion of diagnostic testing relating to the technique (see Table 4). The incidence of failure of completion of diagnostic assessment for an ICUAW syndrome is given in Table 4.

The reasons for failure to complete the clinical assessment were the combination of inadequate patient awakening and comprehension (377/381 [99%] patients), generalised pain (1/381 [0.2%] patients) and patient refusal to cooperate (3/381 [0.8%] patients). The reasons for failure to complete the electrophysiological assessment were inadequate patient compliance (11/17 [65%] patients) and technical problems (6/17 [35%] patients). The electrophysiological diagnostic criteria used across the studies were such that in only four of 17 (24%) studies

Table 2. Incidence of ICUAW.

References	No. of patients	No. with ICUAW	Proportion with ICUAW (%)	95% CI
Ahlbeck et al.[36]	10	5	50	24–76
Ali et al.[28]	136	35	26	19–34
Amaya-Villar et al.[43]	26	9	35	19–54
Bednarik et al.[51]	61	35	57	45–69
Bercker et al.[37]	45	27	60	46–73
Berek et al.[38]	22	18	82	62–93
Brunello et al.[16]	39	13	33	21–49
Campellone et al.[25]	77	7	9	5–18
Coakley et al.[44]	23	12	52	33–71
Coakley et al.[39]	44	37	84	71–92
De Jonghe et al.[20]	95	24	25	18–35
De Letter et al.[45]	98	32	33	24–42
Douglas et al.[40]	25	4	16	6–35
Druschky et al.[41]	28	16	57	39–74
Garnacho-Montero et al.[14]	73	50	69	57–78
Garnacho-Montero et al.[12]	64	34	53	41–65
Hermans et al.[23]	420	188	45	40–50
Hough et al.[32]	30	6	20	10–37
Hund et al.[46]	28	20	71	53–85
Kesler et al.[29]	170	30	18	13–24
Khan et al.[47]	20	10	50	30–70
Latronico et al.[27]	92	28	30	22–41
Leijten et al.[48]	38	18	47	33–63
Mohr et al.[49]	33	7	21	11–38
Nanas et al.[24]	185	44	24	18–30
Routsi et al.[31]	52	14	27	17–40
Schweikert et al.[8]	104	42	40	32–50
Sharshar et al.[15]	115	75	65	56–73
Tepper et al.[26]	22	19	86	67–95
Thiele et al.[50]	19	12	63	41–81
Van den Berghe et al.[22]	405	154	38	33–43
Weber-Carstens et al.[30]	44	25	57	42–70
Witt et al.[42]	43	30	70	55–81
Total	2686	1080	40	38–42

Note: ICUAW, intensive care unit-acquired weakness; CI, confidence interval.

was patient compliance actually required. In these studies, failure of diagnostic assessment because of inadequate compliance was 13% (11/83 patients).

Discussion

There are three main findings from this systematic review. First, the approximate incidence of the ICUAW syndromes as a group was 40% (95% CI 38–42%). Second, the incidence of the ICUAW syndromes when diagnosed clinically was significantly lower (32%, 95% CI 30–35%) than when diagnosed electrophysiologically (47%, 95% CI 45–50%). Finally, the incidence of failure of diagnostic assessment was significantly higher with a clinical diagnostic technique (26%, 95% CI 24–28%) compared to an electrophysiological technique (2%, 95% CI 1–4%).

There are two published systematic reviews in this area,[13,52] the most recent included studies up until 2006. This review adds approximately a further 1200 patients and 12 new studies to this work. The incidence of ICUAW in this review is lower than in those done previously (60%[52] and 46%[13]). The still sizeable incidence of ICUAW reflects the populations studied: those requiring mechanical ventilation beyond approximately seven days, patients with severe sepsis, multiple organ failure or conditions treated with relatively high doses of steroids.

This review is the first to evaluate the incidence of the ICUAW syndromes according to the diagnostic

Table 3. Incidence of ICUAW in subgroups according to diagnostic technique.

Technique	No. of patients	No. with ICUAW	Proportion with ICUAW	95% CI
Clinical diagnosis[8,15,16,20,24,25,28–32,37,40,45,51]	1276	413	32	30–35
Electrophysiological diagnosis[12,14,22,23,26,27,36–39,41–43,45–51]	1591	749	47	45–50
Histological diagnosis[44]	23	12	52	33–71

Note: ICUAW, intensive care unit-acquired weakness; CI, confidence interval.

Table 4. Incidence of failure of completion of diagnostic assessment according to diagnostic technique.

Technique	No. of patients	No. with failed diagnostic assessment	Proportion	95% CI
Clinical diagnosis failure[8,15,16,20,24,25,28,30–32,37,40,45,51]	1488	381	26	24–28
Electrophysiological diagnosis failure[12,14,26,27,36–39,41–43,45–47,49–51]	742	17	2	1–4

Note: CI, confidence interval.

technique. The significant difference in incidence found between the groups diagnosed with a clinical technique compared to an electrophysiological technique may be explained by the techniques themselves (a lack of concordance between clinical and electrophysiological findings[37,51]) and/or by other methodological differences; differing rates of successful completion of testing, variation in the frequency of assessments, the timing of the diagnosis and study population heterogeneity. We did not find a detectable difference in study quality between the clinical and electrophysiological technique groups to explain the difference.

This review found that there was a significant difference in the proportions of patients unable to complete clinical assessment (26%, 95% CI 24–28%) compared to electrophysiological assessment (2%, 95% CI 1–4%). The major cause of this was a lack of patient compliance with clinical assessment. Patients unable to comply with clinical assessment tend to have a higher mortality rate[15,16,20,28] and potentially have greater encephalopathy, both of which are associated with increased incidences of ICUAW.[14,20,23,42,51] The lower incidence of ICUAW in the group diagnosed on clinical assessment is likely to be explained in part by higher rates of incomplete testing.

The strengths of this review include the detailed literature search, the systematic evaluation of included studies with an objective assessment tool and the inclusion of studies utilising the full range of recognised diagnostic techniques. There are limitations to this review. This review was largely the work of a single reviewer with the risk of introducing bias both in the selection of studies to include and in the assessment of included studies. To minimise this risk, clear criteria were set for each domain on the study appraisal form which were used both to assess eligibility for the review and to appraise the quality of the study.

The tool we used to grade the evidence was a modification of the NOS[33] with additional criteria recommended by Altman.[34] The rating scale was modified after a pilot run because the NOS was felt not to adequately discriminate between the different qualities of studies. This is therefore a new tool that is unvalidated and may not have appropriately graded all of the studies. The modified scale did however provide an objective assessment tool that appeared to be appropriate for the majority of the studies.

Conclusion

This systematic review has provided a comprehensive update to those done previously and found that the ICUAW syndromes are common (40%) in the groups of ICU patients requiring more than approximately a week of mechanical ventilation. The incidence of ICUAW varies with the diagnostic technique used, being lower with clinical compared to electrophysiological techniques. Approximately a quarter of patients will not be able to comply with clinical evaluation and this may be responsible for underreporting of this condition. Further research is required to validate the 2009 consensus diagnostic criteria and to identify the optimal method and time point for identifying this problem to then allow interventions to be evaluated and introduced.

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