FLEX CEUs

ICU-Acquired Weakness Therapy Considerations

Physiotherapy management of intensive care unit-acquired weakness

KEY WORDS

Physical therapy
Intensive care
Critical care
Weakness
Early mobilization

Introduction

Intensive care unit-acquired weakness (ICUAW) is a common condition in critically ill patients who are mechanically ventilated for prolonged periods of time.[1] Only recently have mechanistic studies shown that muscle atrophy and loss of muscle mass develop rapidly during critical illness – within hours of the patient being intubated and mechanically ventilated.[2] Physiotherapists play an integral role in the prevention and treatment of ICUAW within the intensive care unit (ICU), with studies showing benefit from early mobilisation and inspiratory muscle training for patients in the ICU to improve duration of weaning and functional independence at hospital discharge.[3,4] Most importantly, as survival from ICU increases, physiotherapists will have a greater role in the management of ICUAW after discharge from ICU and hospital.

This review summarises the pathophysiology of ICUAW; the diagnosis during critical illness; the respiratory and musculoskeletal consequences of ICUAW; the burden of ICUAW on survivors of critical illness and their families; strategies to prevent and manage ICUAW, with a focus on specific physiotherapy interventions during critical illness; and future directions for research and practice.

What is intensive care unit-acquired weakness?

ICUAW is a clinical syndrome of generalised muscle weakness that develops while a patient is critically ill, and for which there is no alternate explanation other than the critical illness itself.[1,5] ICUAW is caused by different pathologies, including critical illness myopathy, polyneuropathy or a combination of both.[6–8] It differs from other neuromuscular disorders in the ICU in that facial and ocular muscles are rarely involved, creatine kinase levels are not elevated and demyelination is not a feature.[1] In a recent binational, multicentre cohort study, ICUAW was present in more than 50% of patients at ICU discharge who were mechanically ventilated for greater than 48 hours.[3]

Diagnosis

The diagnosis of ICUAW requires a critical illness, or an illness of a very high severity with prolonged organ support, that is usually associated with a period of protracted immobilisation.[5,9] Key clinical signs that support a diagnosis of ICUAW include the presence of normal cognition, sparing of the cranial nerves, and the presence of symmetrical flaccid weakness. In an official American Thoracic Society Clinical Practice Guideline, ICUAW was reported to be more common in patients with severe sepsis, prolonged mechanical ventilation, or difficulty with liberation from mechanical ventilation.[5] There was no consensus on the approach to diagnosis of ICUAW, including how or when the diagnosis can be made.

Bedside examination of the ICU patient may be complicated by the use of sedatives, neuromuscular blockers and delirium. In clinical practice, physical examination of the muscle groups is usually performed using the Medical Research Council (MRC) Manual Muscle Test, which is dependent on patient effort and cooperation.[10,11] This scale evaluates muscle strength with a score ranging from 0 (no muscle contraction) to 5 (full strength) (Table 1). Physical examination of three muscle groups in each of the upper and lower limbs results in a composite or sum score of the MRC out of 60. Clinically detectable muscle weakness has been defined as 80% of the MRC sum score (ie, a score of < 48 out of a total score of 60). This method has been proven reliable in a cooperative patient.[12,13] Other methods of volitional muscle strength testing that are commonly used in the ICU include handheld dynamometry.[13,14] In a prospective, multicentre cohort study, hand-held dynamometry was used to identify patients with ICUAW and was independently associated with increased hospital mortality.[14]

Pathophysiology

Muscle changes rapidly in the early days of critical illness.[2,15–17] This acute phase response is demonstrated by a reduced ratio of protein to DNA, depressed muscle protein synthesis and a catabolic

Table 1
Medical Research Council (MRC) manual muscle testing for muscle strength.[9]

MRC Grade	Clinical presentation is graded on patient effort
0	No movement is observed.
1	Only a flicker or a trace of movement is seen or felt in the muscle or fasciculations are seen in the muscle.
2	Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane.
3	Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side.
4	Muscle strength is reduced but muscle contraction can still move joint against resistance.
5	Muscle contracts normally against full resistance.

state of proteolysis, which starts within the first days of critical illness and may be accompanied by generalised weakness.[2,18–20] In addition, the interaction of bed rest and critical illness appears to result in more significant muscle loss than bed rest alone.[17,21,22] There is evidence of loss of myosin and membrane excitability. Overall, studies have shown that ICUAW results in decreased muscle protein synthesis, increased muscle catabolism, and decreased muscle mass with decreased force generation. However, there may be significant overlap in biological processes that regulate both muscle mass and nerve contractility, and ICUAW encompasses both critical illness polyneuropathy and myopathy; it therefore may be accompanied by axonal nerve degeneration.[23,24] Additionally, there may be differences between the early and late stages of skeletal muscle dysfunction that should be considered in clinical practice.[20]

Risk factors for intensive care unit-acquired weakness

Bed rest

Both the pathophysiological mechanisms and risk factors are multifactorial in the development of ICUAW in critically ill patients (Box 1). As previously mentioned, in a large multicentre cohort study of 222 patients with acute lung injury, duration of bed rest was the only consistent factor that was associated with the development of ICUAW.[22] It is likely that a combination of both disuse atrophy and inflammation with muscle catabolism results in ICUAW; this challenges the current conventional model of care, in which patients are sedated and immobilised for prolonged periods during the ICU stay.

Sepsis and multi-organ failure

During critical illness, a catabolic state with muscle wasting and systemic inflammation occurs, particularly in patients with sepsis.[25] Two studies have reported a significant association between the presence and duration of systemic inflammatory response syndrome and ICUAW in the first week of ICU.[26,27] Patients diagnosed with sepsis have consistently been identified as having long-term functional disability and should be assessed early in the ICU stay for ICUAW.[28,29] In a landmark publication of patients with acute respiratory distress syndrome (ARDS), multiple organ failure was associated with long-term physical dysfunction and poor health-related quality of life for up to 5 years.[30]

Box 1. Predictors of ICU-acquired weakness.

Intrinsic predictor variables	Intensive care predictor variables
• Age	• Hyperglycaemia
• Medical comorbidities	• Sepsis and inflammation
• Frailty	• Corticosteroids
• Level of independence at admission	• Prolonged use of neuromuscular blockers
• Number of medical comorbidities, including mental health issues and musculoskeletal pathology	• Duration of ventilation
	• Duration of bed rest
	• Duration of ICU stay

ICU = intensive care unit.

Hyperglycaemia

Hyperglycaemia is the most consistently identified risk factor for ICUAW;[31] however, in a large multicentre Phase-III study of intensive glucose control compared with standard care led by investigators in Australia, tight glycaemic control was shown to increase the odds ratio for death.[32] Rather than managing patients with tight glycaemic control, critically ill patients, particularly those with hyperglycaemia, should be assessed for ICUAW and managed with early intervention.

Corticosteroids

Following a prospective cohort study that demonstrated an association between the use of corticosteroids and ICUAW,[8] a number of studies, including a systematic review, have failed to support this association.[31] Despite the current evidence, the use of corticosteroids remains controversial in ICU, with concerns about increased risk of ICUAW.

Neuromuscular blockers

Despite early concerns about the use of neuromuscular blockers in the ICU, several prospective trials, a large, multicentre, randomised, controlled trial and a recent systematic review have failed to show an association between their use and ICUAW.[33,34] Considering the mortality benefit shown in patients with ARDS with the early use (first 48 hours) of neuromuscular blockers to reduce lung injury, the use of these medications should be considered on an individual basis. It is possible that prolonged use of neuromuscular blockers in ICU patients has a different effect to short-term use.

Burden of intensive care unit-acquired weakness

Duration of mechanical ventilation and length of ICU stay

Prolonged duration of mechanical ventilation and ICU stay is a common manifestation of ICUAW. This can occur as a result of weakness in both the diaphragm and the muscles of the chest wall that requires prolonged mechanical support. In a systematic review of ICU patients diagnosed with sepsis, 12 of 13 studies demonstrated that ICUAW was associated with prolonged mechanical ventilation.[25]

Survival and health-related quality of life

Severe weakness is common among survivors of critical illness, and it may persist for years.[22,30] In a recent cohort study conducted in 12 ICUs in Australia and New Zealand, over 50% of patients who received mechanical ventilation for $>$ 48 hours and survived to ICU discharge were found to have ICUAW.[3] The presence of ICUAW at ICU discharge was associated with poor long-term outcome, including increased 90-day mortality compared with patients who did not have ICUAW.[3] This has been confirmed in international cohort studies where increased weakness at discharge was associated with increased risk of mortality at 12 months.[35] ICUAW has also been associated with poor health-related quality of life in cohort studies in the years following critical illness.[35–37] In one cohort study of 13 ICUs in Baltimore, USA, duration of bed rest was the only factor consistently associated with weakness after discharge from hospital. At 2 years, patients with ICUAW had reduced health-related quality of life and physical function

(measured with 6-minute walk test) compared with patients with normal strength.[22]

It has been rare for studies of critically ill patients to concurrently assess for both functional and pathophysiological changes; therefore, these results should be interpreted cautiously.[38] There are still limitations in the understanding of mechanistic changes in muscle structure and function during critical illness and their potential for effects on long-term outcomes, given the many confounding factors that may affect patient recovery.[39]

Management of intensive care unit-acquired weakness

A summary of interventions used in the management of ICUAW, along with the level of evidence that underpins their use, is provided in Figure 1.

Inspiratory muscle training

Mechanical ventilation is a major factor in the disuse atrophy and deconditioning of a patient's respiratory muscles because it may replace the spontaneous respiratory muscle effort. The diaphragm in particular responds to invasive mechanical ventilation with atrophy and proteolysis. Respiratory muscle weakness may increase the duration of mechanical ventilation and prolong the period of weaning from mechanical ventilation.[40]

Inspiratory muscle training has been used in an attempt to improve diaphragmatic muscle strength in patients with ICUAW. Evidence from a recent systematic review of 10 studies (including 394 participants) of inspiratory muscle training achieved by threshold pressure training or ventilator sensitivity adjustment showed that the training significantly improved maximal inspiratory pressure (MD 7 cmH_2O, 95% CI 5 to 9), rapid shallow breathing index (MD 15 breaths/minute/l, 95% CI 8 to 23) and weaning success (RR 1.34, 95% CI 1.02 to 1.76).[41] However, difficulty in weaning is a key feature in ICUAW and in this systematic review there was no difference in the reported duration of weaning that was pooled from six of the studies (MD 1.7 days, 95% CI –0.3 to 3.6). The limitations of this systematic review included differences between the studies in eligibility criteria, training regimens and usual care (such as standardised weaning and sedation protocols), which may have influenced the results.[41]

In addition to this systematic review, there is a recently published single-centre, randomised, controlled trial of inspiratory muscle training in patients who had been successfully weaned from mechanical ventilation for > 48 hours.[42] In this study, 34 patients were randomly allocated to receive inspiratory muscle training once daily for 5 days per week for 2 weeks as well as standard care (intervention), and 36 patients were randomly allocated to standard care only (control). The primary outcome measures were inspiratory muscle strength and fatigue resistance index at 2 weeks after enrolment. Similar to the previously reported meta-analysis, the intervention group in this trial demonstrated greater improvements in inspiratory muscle strength (MD of the maximal inspiratory pressure, 11% predicted, 95% CI 2 to 20) but no difference in the fatigue resistance index (MD 0.02, 95% CI –0.15 to 0.12). Although inspiratory muscle strength was improved, there was a concerning signal for higher in-hospital mortality in the intervention group (4/34 versus 0/36, $p = 0.051$). There were no between-group differences for measures of physical function, dyspnoea, length of stay or ICU readmission. Survivors reported improved health-related quality of life (measured with the EuroQol five dimensions questionnaire, EQ-5D-3L) at 2 weeks after enrolment compared with at the time of enrolment, with the improvement being significantly greater in the experimental group (MD between groups 12%, 95% CI 1 to 23).[42] When this trial of IMT *after* mechanical ventilation is combined with previous studies of inspiratory muscle training *during* mechanical ventilation in a meta-analysis, the body of evidence suggests that there is no overall increased risk of mortality with inspiratory muscle training (Figure 2; for a detailed forest plot, see Figure 3 on the eAddenda).[98–101] Further studies are required to confirm the safety of inspiratory muscle training *after* patients are weaned from mechanical ventilation.

In summary, current evidence for the effects of inspiratory muscle training in patients during mechanical ventilation is inconsistent, but does suggest a benefit for improved inspiratory muscle strength in ventilated patients. There is significant heterogeneity in the enrolment criteria, timing of intervention, the training regimen, the control group and the outcomes measured between the reported studies.[41] Importantly, improved muscle strength has not translated into evidence of improved hospital outcomes with regards to duration of weaning or length of stay in ICU or hospital. In the recent randomised, controlled trial of inspiratory muscle training after weaning from mechanical ventilation,[42] improvements reported in health-related quality of life were measured within 2 weeks of the intervention,[42] and longer term outcomes need to be measured in a large trial.

Cycle ergometry

A cycle ergometer is a stationary bicycle that allows patients to receive passive, active-assisted, and active-resistive exercise. In the ICU, cycle ergometry may be used with sedated, immobile, or awake patients to provide range of motion and muscle strength training whilst patients are in bed.[43,44] In a randomised trial involving 90 mechanically ventilated patients with prolonged ICU stays in Belgium, a 20-minute session of leg cycling on 5 days per week in addition to standard care resulted in increased isometric quadriceps force, higher self-perceived functional status, and increased functional exercise capacity, as measured by the 6-minute walk test at hospital discharge.[45] There are several pilot studies underway testing the use of cycle ergometry in the ICU, which investigate its effect on muscle morphology,[46] strength and physical function.[47] Further research is required to determine the utility of cycle ergometry in the ICU to improve patient-centred outcomes.

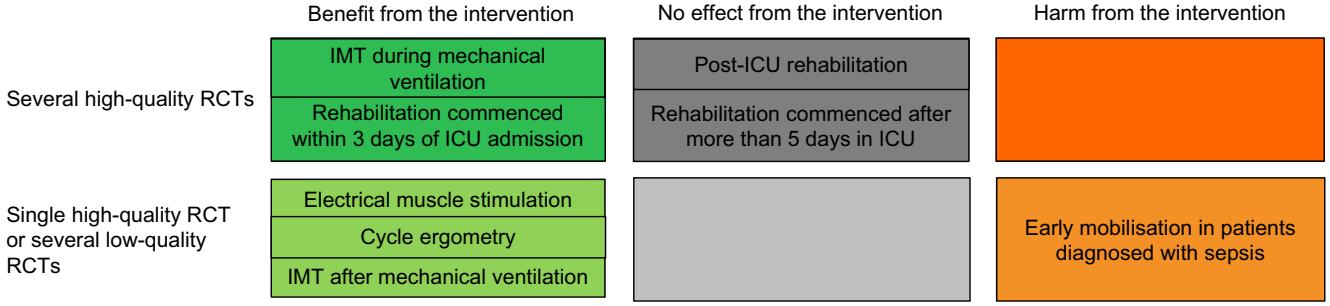

Figure 1. Interventions for management of intensive care unit-acquired weakness, with associated levels of evidence.
ICU = intensive care unit, IMT = inspiratory muscle training, RCT = randomised controlled trial.

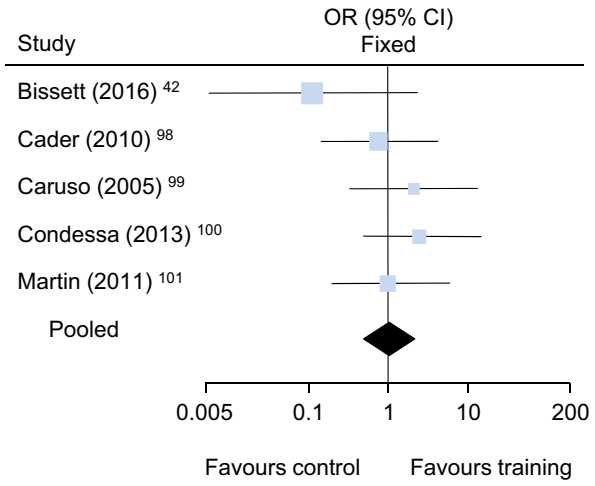

Figure 2. Odds ratio (95% CI) of the effect of inspiratory muscle training on survival in the intensive care unit. The odds of survival did not significantly differ between those who did and did not receive the training.

Post-ICU rehabilitation

In 2009, the National Institute for Health and Care Excellence (NICE) published guidelines that recommended rehabilitation as a key strategy in recovery for adult survivors of critical illness.[48] These guidelines have been widely cited[49–51] despite the lack of evidence to support post-ICU rehabilitation (ward-based, outpatient-based or home-based) to improve outcomes in this cohort.[52–54]

A Cochrane review of exercise rehabilitation following ICU discharge for recovery from critical illness assessed the effectiveness of exercise programs on functional exercise capacity and health-related quality of life.[55] Six trials were included, providing data on 483 adult ICU survivors. Interventions were delivered on the wards or in the community, and the duration of the interventions varied according to hospital length of stay, with a maximum of 12 weeks of rehabilitation after ICU discharge. The studies included a range of interventions, such as arm and leg cycling exercises, walking, strengthening exercises, provision of self-help manuals and programs that were based in physiotherapy outpatient departments that included a combination of functional and strengthening exercises and education. All of the studies measured functional exercise capacity, but there was significant variability in the outcome measures and data reported, and overall the quality of the evidence was low.[55] The review was unable to determine an overall result for the effects of an exercise-based intervention, with three studies reporting an improvement in functional exercise capacity and three studies reporting no effect. Due to the different outcome measures used in the studies, the data were unable to be meta-analysed. Importantly, the authors reported a lack of acknowledgement of standard practice, which might have affected the results. For example, the usual level of rehabilitation and exercise in standard practice may have influenced the results of the studies.[55]

Since the publication of that Cochrane review, a large, randomised, controlled trial of post-ICU rehabilitation in the UK has been published.[54] Walsh and colleagues randomised 240 patients who had received at least 48 hours of mechanical ventilation to receive a complex intervention led by a rehabilitation coordinator that included additional physiotherapy, nutritional review, individualised goal setting and illness-specific information. There were no between-group differences for the primary outcome measure at 3 months (Rivermead Mobility Index) or for any other functional or quality of life outcomes at any time point. The study found that patients in the intervention group reported greater satisfaction with physiotherapy, nutritional support, coordination of care, and information provision. This study highlights the importance of coordination of care after critical illness in this cohort.

Preventing intensive care unit-acquired weakness

Electrical muscle stimulation

Electrical muscle stimulation (EMS) has been investigated as a treatment for the prevention of ICUAW.[56,57] It involves placing transcutaneous electrodes over the skin, which activate the underlying nerves to produce an isometric muscle contraction.[43,58] The treatment involves minimal joint movement and does not require patient interaction.[56,57]

Three systematic reviews (including eight randomised trials) have assessed the use of EMS in the critically ill population.[59–61] The EMS treatments provided across the studies were 30 to 60 minutes in duration, daily, for at least 4 days. The exact treatment protocols varied in the muscles that were stimulated, the duration of therapy, and the pulse characteristics and impulse intensity of the EMS.[59–61] Meta-analysis was only completed in one of the systematic reviews, with the pooled results of two studies showing increased quadriceps femoris strength in the EMS group compared with the control group, measured with the MRC scale (MD 0.77, 95% CI 0.19 to 1.40, n = 80).[59] In these studies, patient acuity was measured with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Individually, one study with lower patient acuity (median APACHE II scores of 16) demonstrated greater preservation of muscle mass with EMS (8 to 14% reduction),[62] whilst two studies with higher patient acuity (median APACHE II scores of 20 and 25) demonstrated a greater degree of muscle mass loss and that EMS did not preserve muscle mass (16 to 20% reduction).[63,64] One study demonstrated significantly greater quadriceps muscle thickness in the EMS group (+4.9%) compared with the placebo (–3.2%) using EMS in long-stay ICU patients,[65] and one study demonstrated increased rates of ICUAW in the placebo group (39%) compared with the EMS group (13%).[66] Routsi and colleagues also demonstrated a shorter weaning period from mechanical ventilation in the EMS group (median 1, range 0 to 10) compared with the control group (median 3, range 0 to 44, $p = 0.003$), and a shorter period from weaning from mechanical ventilation to ICU discharge in the EMS group compared with the control group (median 4 days, range 0 to 16, versus 6 days, range 0 to 41, respectively, $p = 0.003$).[66]

There are several concerns reported in the systematic reviews about the included studies. First, the studies visually determined the muscle contraction, which may have been unreliable.[60] There was a lack of high-quality studies and some studies used higher pulse durations and intensity than recommended by some authors,[67] which may have caused fatigue and skewed the results.[59] There was a large amount of heterogeneity in the treatment protocols and outcome measures used, which limited meta-analysis. This suggests that researchers are not yet sure what is important in terms of procedure and outcome measures for EMS.[59]

The results of these studies indicate that EMS might be an attractive intervention for critically ill patients and it may have the ability to maintain muscle mass and strength in the ICU setting,[59] particularly in long-stay ICU patients and those with lower levels of acuity. Further large, randomised, controlled trials need to be completed to determine the overall effect of EMS and the most appropriate training regimen.[60]

Mobilisation in the ICU

Mobilisation of mechanically ventilated patients in the ICU has been shown to be feasible and safe.[4,68,69] Numerous randomised trials have investigated the use of early mobilisation in the ICU, with the intervention starting within 3 days of ICU admission[70–73] or starting later in the ICU admission (after 5 days).[74,75] It is

important to note that the studies report different periods with regards to time from ICU admission to the start of early mobilisation, and time from randomisation to the start of rehabilitation, which might be different if there is a long period between ICU admission and randomisation into the study.

The results of the individual studies are conflicting, with some studies reporting no benefit,[74–76] whilst others report improved function at hospital discharge,[73,77] greater independent walking distance,[73,78] higher mobility milestones,[71,77] decreased duration of mechanical ventilation,[73,79] increased muscle strength[80] and improved quality of life of survivors[72] favouring the intervention group. One study reported significantly lower 6-minute walk test results in the early rehabilitation group compared with the control at ICU discharge (MD 42 m, 95% CI 4 to 79).[74] Whilst previous systematic reviews[81,82] have assessed the impact of mobilisation in the ICU, they have had limited ability to complete meta-analysis due to the heterogeneity in the study designs, in particular the outcome measures used and the timing of these assessments. To date, the significant results supporting mobilisation in the ICU with improvements in function, mobility and quality of life have been reported in studies that commenced the intervention early in the ICU stay.[71–73,77] This may demonstrate a greater ability for early mobilisation to *prevent* ICUAW and long-term functional impairments than to treat muscle weakness once it is established.[83]

A recent systematic review and meta-analysis of early rehabilitation during ICU stay on functional status demonstrated a greater probability of walking without assistance at hospital discharge in the early mobilisation group compared with the control group (pooled RR 1.42, 95% CI 1.17 to 1.71, four studies).[81] This systematic review and meta-analysis also reported the risk ratio for ICUAW between the intervention and control groups (pooled RR 0.75, 95% CI 0.51 to 1.09, three studies). However, this analysis pooled studies that included both electrical muscle stimulation and early mobilisation, and measured ICUAW at different points in the patient's trajectory. An updated pooled analysis of the proportion of patients who developed ICUAW in studies of early mobilisation demonstrates a lower risk of ICUAW in the early mobilisation group compared with the control group (OR 0.54, 95% CI 0.32 to 0.91) (Figure 4; for a detailed forest plot, see Figure 5 on the eAddenda).[71,73,74] The sensitivity analysis demonstrates that the results are driven by the two studies that commenced mobilisation within 3 days of ICU admission.[71,73]

We need to carefully consider strategies for retention of patients into studies that measure long-term outcomes after critical illness, including registry linkages.[84,85] To this end, there are excellent resources available from experts in the field that should be considered for use in ICU studies requiring follow-up.[86] Several recent studies of mobilisation and rehabilitation that measured long-term recovery after hospital discharge have demonstrated that a large number of participants were lost to follow-up or withdrew from the trial.[54,74,75,77] Finally, there is an urgent need for a large trial to confirm the impact of mobilisation in the ICU on patient-centred, long-term outcomes.[83,84] In some other areas of clinical practice, early mobilisation of acutely unwell patients has not demonstrated improved patient-centred outcomes,[87,88] and this may be true in specific ICU cohorts, for example patients with severe sepsis.[72]

Future directions for research and practice

There are several important considerations for the physiotherapy management of patients in the ICU who are at risk of developing ICUAW or who have been diagnosed with ICUAW. One of the criticisms of previous randomised trials assessing strength and function of patients in the ICU is the heterogeneous population. There is no measurement of baseline function that may affect the ability to recover, with evidence that patients who are older and with comorbid conditions are less likely to respond to interventions.[89–91]

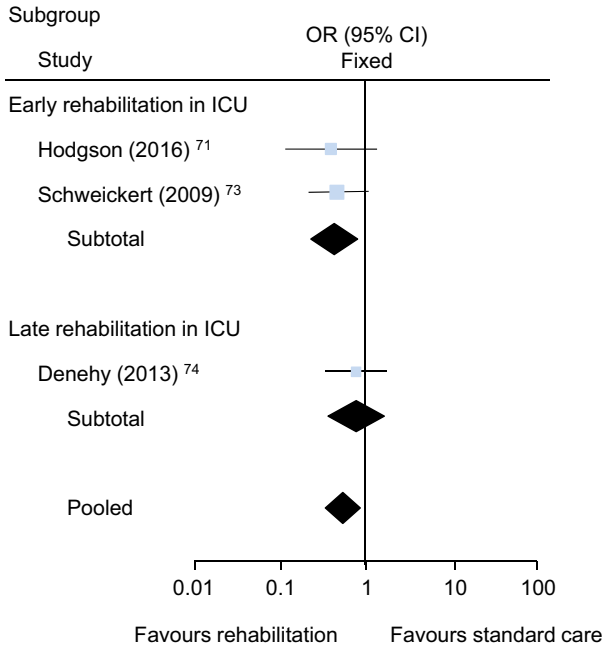

Figure 4. Odds ratio (95% CI) of ICUAW with or without mobilisation and rehabilitation in the ICU. Overall, mobilisation and rehabilitation reduced the odds of ICUAW. When studies were subgrouped into mobilisation and rehabilitation started within 3 days of admission to ICU (early) or after more than 5 days in ICU (late), the odds of ICUAW were only significantly reduced with early mobilisation and rehabilitation compared with standard care. ICU = intensive care unit, ICUAW = Intensive Care Unit Acquired Weakness.

Similarly, the risks and benefits for specific diagnostic groups are currently unknown. One study demonstrated increased mortality in septic patients who received early mobilisation[72] (and direct communication with authors). Another study demonstrated increased mortality with inspiratory muscle training commenced after weaning from mechanical ventilation.[42] The study by Schweickert et al. that demonstrated improved recovery at hospital discharge included a heterogeneous population, but the participants were all functionally independent prior to ICU admission.[73] Another study in the surgical population demonstrated decreased length of hospital stay, with patients also functionally independent prior to ICU admission.[77] Therefore, there is an urgent need for future studies to identify responders and non-responders to mobilisation and rehabilitation in the ICU.[90,92]

Increasingly, physiotherapists have focused on exercise-based interventions in the ICU, including both bed exercises and mobilisation out of bed.[81,82] These have been shown to be safe and effective during the ICU stay[4,68,93] and there is evidence that they may reduce hospital length of stay and improve functional independence at hospital discharge.[73] This appears to be more apparent in studies that randomised patients early (within 3 days) of the ICU stay.[71–73] However, there is an urgent need for research that helps us to understand the risks versus the benefits of early mobilisation and rehabilitation on long-term outcomes and patient recovery beyond the hospital stay.[84,85] Until the long-term outcomes are assessed in an adequately powered, multicentre trial, the safety of the intervention remains unclear.

In the past 12 months, several new randomised, controlled trials have assessed the effect of physiotherapy and early rehabilitation in patients with acute respiratory failure.[75–77] Whilst the number of studies in this field is increasing, there is no clear evidence of a dose-response in critically ill patients. Few of these studies have published precise data on the dosage of exercise per patient. Future studies could improve the understanding of the dose-response by providing this valuable information. This would require information about the timing and duration of exercise (minutes) and the type of exercise delivered, using a valid

measurement tool. There is an active international research agenda to develop a core set of outcome measures for patients after ICU.[94–96] This is urgently required because the larger trials that have measured long-term outcome have included different outcome measures of strength, physical function and health-related quality of life, therefore limiting the ability to pool the results.[97] In the future, ICU research assessing strength and function should include a core set of outcome measures to allow comparison between studies.[94]

In the clinical setting, physiotherapists have a growing body of evidence to guide practice when treating patients during critical illness (Figure 1). ICUAW is common and occurs rapidly during the ICU stay; however, the evidence for important benefits of early physiotherapy interventions in ICU is not strong.[9] It is possible that early interventions, including inspiratory muscle training, early mobilisation and cycle ergometry, reduce ICUAW and improve independence at hospital discharge; however, currently it is unclear which intervention, timing and dosage is best to prevent or treat ICUAW.[83] There are several ongoing studies that will inform long-term outcomes for patients in this area of practice in the future.