Muscle wasting in the critically ill patient: how to minimise subsequent disability

Abstract

Muscle wasting in critically ill patients is the most common complication associated with critical care. It has significant effects on physical and psychological health, mortality and quality of life. It is most severe in the first few days of illness and in the most critically unwell patients, with muscle loss estimated to occur at 2–3% per day. This muscle loss is likely a result of a reduction in protein synthesis relative to muscle breakdown, resulting in altered protein homeostasis. The associated weakness is associated with in an increase in both short- and long-term mortality and morbidity, with these detrimental effects demonstrated up to 5 years post discharge. This article highlights the significant impact that muscle wasting has on critically ill patients' outcomes, how this can be reduced, and how this might change in the future.

Key words: Critical care; Critical illness; Intensive care; Mobilisation; Muscle wasting; Rehabilitation

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Introduction

In 1892 William Osler first described the 'rapid loss of flesh' seen in patients suffering from severe sepsis. To this day this same process continues to affect critical illness survivors across the world, while remaining under-recognised.

Muscle wasting is the most common complication associated with critical care. It affects more than 50% of critically ill patients, significantly higher than the incidence of other commonly quoted critical illness-related complications such as venous thrombosis (30%), ventilator-associated pneumonias (25%) and central line infections (0.058%) (De Jonghe et al, 2002; Pronovost et al, 2006; Boddi et al, 2010).

Attempts to quantify the magnitude of muscle loss seen have commonly looked at changes in size of the rectus femoris muscle in critically ill patients. Reduced quadriceps cross-sectional area and strength are associated with reduced exercise tolerance and poorer prognosis (Swallow et al, 2007). Thus changes in rectus femoris cross-sectional area may act as a surrogate indicator for muscle wasting and aid prognostication. During critical illness an average of 12.5% decrease in muscle cross-sectional area is seen over the first week, progressing to 17.7% at 10 days (Puthucheary et al, 2013).

This muscle loss is most severe in patients with multi-organ failure (-15.7% vs -3% in single organ at day 7), rising to 20.3% when four or more organs are affected (Puthucheary et al, 2013). On histological analysis of the muscle, more than half of the samples demonstrate myofibre necrosis (Puthucheary et al, 2013).

Multiple studies have reinforced the association between critical illness and muscle wasting. A 2015 study showed a 30% reduction in rectus femoris cross-sectional area and associated weakness in ventilated patients at day 10 (Parry et al, 2015) and further research has demonstrated this in patients receiving extra-corporeal membranous oxygenation (a 19% reduction in rectus femoris cross-sectional area at day 10) (Hayes et al, 2018). This rapid loss of muscle is the major driver of the umbrella syndrome of intensive care unit-acquired weakness. Other components include critical illness myopathy, critical illness polyneuropathy, and critical illness polyneuromyopathy. While often referenced as separate entities, in clinical practice these are likely overlapping pathologies and are rarely seen in isolation. They are all acquired pathologies associated with critical illness, and have a reported prevalence of more than 70% in the most critically unwell patients (Linos et al, 2007).

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Critical illness myopathy is a primary symmetrical myopathy associated predominantly with proximal muscle weakness and associated muscle atrophy. In contrast, critical illness polyneuropathy is a primary symmetrical neuropathy, with predominantly distal weakness, sensory loss and limited atrophy (Shepherd et al, 2017). Critical illness polyneuromyopathy has been described as a combination of the critical illness myopathy and critical illness polyneuromyopathy, with both a symmetrical myopathy and neuropathy present. Similarly to critical illness myopathy, critical illness polyneuromyopathy is also characterised by primarily proximal weakness; however, as in critical illness polyneuropathy, predominantly distal sensory loss is seen. In the advanced stages, all three of these pathologies are associated with reduced deep tendon reflexes, physical weakness, and prolonged mechanical ventilation (Shepherd et al, 2017). Diagnostic testing is often challenging and unreliable, involving a combination of electromyography, nerve conduction studies and physical scoring systems, the latter commonly significantly confounded by patient sedation.

Separating these syndromes out is not clinically useful currently, and nerve conduction testing and electromyography can be technically difficult in the critically ill patient (eg secondary to oedema). In the early stages of critical illness, electromyography or nerve conduction study findings are universally abnormal and unrelated to subsequent weakness (Shepherd et al, 2017). Critical illness polyneuropathy is the most uncommon, but should be looked for in the setting of persistent disability, which these patients are at risk of (Shepherd et al, 2017). Testing for non-excitable membrane may be the exception to this, in that it predicts the development of intensive care unit-acquired weakness (Weber-Carstens et al, 2009), but this technique is primarily used in research and the neurological components of intensive care unit-acquired weakness will not be covered in this article.

At hospital discharge 38% of these patients still demonstrate significant muscle weakness, with increased fat to lean muscle mass percentage seen at 12 months post discharge, associated with an increased 5-year mortality (Dinglas et al, 2017). Even relatively young patients with few comorbidities still suffer from physical limitation, reduced quality of life and psychological sequela 5 years on from their initial illness (Pfoh et al, 2016).

These disabilities result in a significant financial burden. The annual health care-related cost per critical illness survivor is three times that of healthy working adults, and comparable to patients living with chronic diseases (Herridge et al, 2011). With only 27% of critical care services in the UK offering follow-up service post hospital discharge (National Institute of Health and Care Excellence, 2017), with lack of funding the most quoted reason, the true cost within the UK remains unknown (Connolly et al, 2014).

Pathophysiology

The over-arching pathophysiology behind muscle wasting in critically illness is altered protein homeostasis: reduced muscle protein synthesis and increased muscle protein breakdown. Multiple factors affecting protein homeostasis exist in the critically ill patient, both extrinsic (inflammation, inadequate protein, sedation and immobilisation) and intrinsic (old age, chronic diseases, low muscle mass) (**Figure 1**). Understanding how this balance is affected by critical illness is important to minimise harm from critical care interventions, as is understanding what (currently) cannot be overcome.

Altered protein homeostasis

In healthy humans, the interplay between muscle protein synthesis and muscle protein breakdown results in balanced protein homeostasis. Muscle protein synthesis is the facilitative, or major process altered by all stimuli in humans. Following an anabolic stimulus (such as amino acid ingestion), a relative increase in muscle protein synthesis is observed, surpassing muscle protein breakdown and resulting in a positive balance and net muscle gain.

If an anti-anabolic stimulus is instead applied (such as systemic inflammation or immobilisation), there may be a significant reduction in muscle protein synthesis, relative to muscle protein breakdown, resulting in a negative total balance and thus muscle loss. Exercise alone is a catabolic stimulus, until amino acid ingestion occurs, resulting in a net anabolic gain (Tipton and Wolfe, 2001).

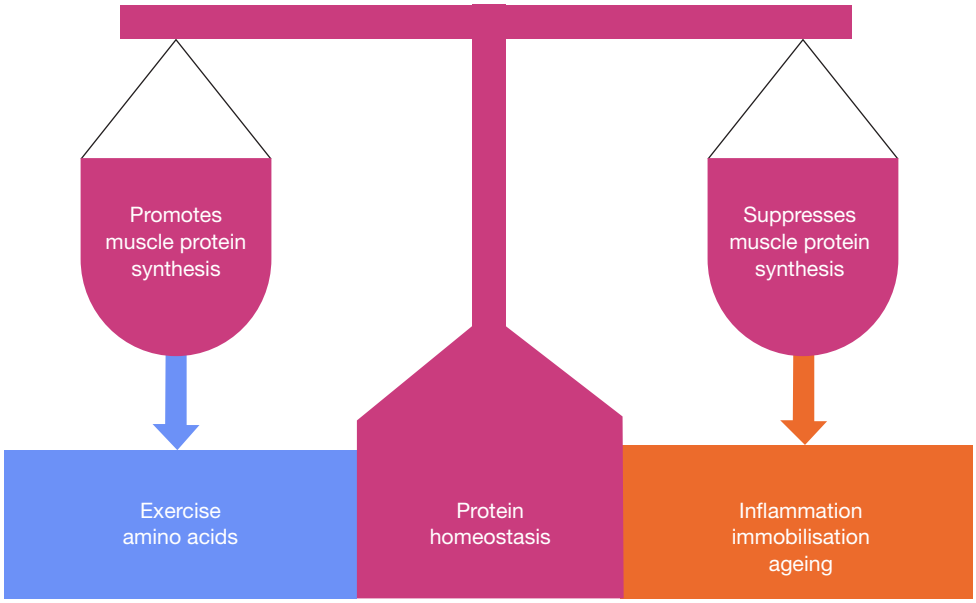

Figure 1. Muscle protein homeostasis.

The rate of muscle loss is highest in the early stages of the disease, with rates of protein synthesis on the day of admission being comparable to fasted healthy controls (despite the establishment of feeding), and slowly resolving over the following weeks. Muscle protein breakdown only increases in prolonged critical illness by day 30, as the usual rate of de novo protein synthesis resumes (Gamrin-Gripenberg et al, 2018), maintaining a net catabolic state. While it remains unclear as to the exact mechanism underpinning suppressed muscle protein synthesis, current data support both metabolic and inflammatory pathologies. Protein synthesis is highly energy dependent, and a combination of decreased mitochondrial biogenesis, dysregulated beta oxidation (Puthucheary et al, 2018), and impaired GLUT-4 translocation leads to a bioenergetics crisis and decreased intramuscular ATP content (Weber-Carstens et al, 2013; Puthucheary et al, 2018). Current nutritional therapies are unable to address this as a result of both impaired glucose uptake and downregulated fat oxidation. Inflammation is a well-described anti-anabolic stimulus (Vesali et al, 2010). Intramuscular inflammation has been repeatedly described in the critically ill patient (Puthucheary et al, 2018). Intramuscular inflammation (and hypoxic signalling) additionally impairs glucose metabolism by the Pasteur effect (**Figure 2**) (Puthucheary et al, 2018).

Who is at risk?

Owing to the significant short- and long-term impact that critical illness muscle wasting has on patients, identifying those at higher risk may enable clinicians to target these groups with aggressive management and early mobilisation.

Critical illness-specific risk factors

A broad range of studies has demonstrated a fairly consistent list of predisposing risk factors.

Uniformly it appears patients with the most severe illness are those who suffer the highest degree of muscle loss, myopathy and neuropathy. These are typically the patients in multi-organ failure, with those suffering 4-organ failure experiencing greater muscle wasting than those with 2–3 organ failure (Puthucheary et al, 2013).

The use of the APACHE II score and the presence of systemic inflammatory response syndrome have also demonstrated this effect, with higher scores and the presence of systemic inflammatory response syndrome correlating with increased risk of myopathy and neuropathy (De Jonghe et al, 2002). Similar associations have been seen with biochemical and physiological markers, such as raised serum C-reactive protein level,

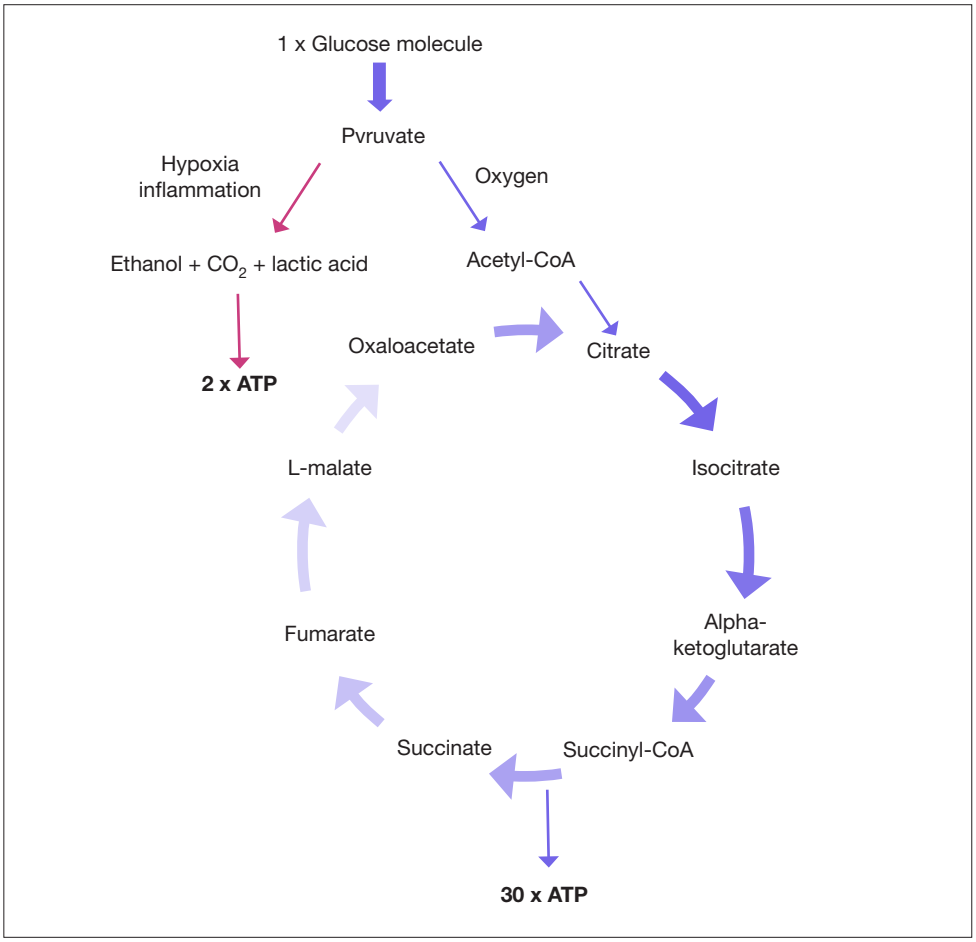

Figure 2. The Pasteur effect refers to the inhibition of anaerobic metabolism with the presence of oxygen, resulting in improved efficiency of glucose metabolism with the production of approximately 30 adenosine triphosphate (ATP) molecules for every one glucose molecule by facilitating oxidative phosphorylation. The presence of hypoxia or inflammation results in inhibition of pyruvate dehydrogenase kinase, a less efficient system and the production of only two ATP molecules.

low partial pressure of oxygen:fraction of inspired oxygen (PaO_2/FiO_2) ratios and low serum bicarbonate level (Puthucheary et al, 2013).

Contrary to earlier reports, the use of neuromuscular blocking agents is not associated with the development of intensive care unit-acquired weakness (Papazian et al, 2010; Puthucheary et al, 2012). These earlier case reports were confounded by high dose corticosteroid use, and sedation and ventilation practices not used in modern critical care. The only randomised controlled trial to test this showed no increased incidence of intensive care unit-acquired weakness (Papazian et al, 2010) even with corticosteroids (Puthucheary and Montgomery, 2010). Use of neuromuscular blocking agents may even be beneficial, as a decrease in circulation inflammatory markers was noted (Papazian et al, 2010).

Pre-existing risk factors that are non-modifiable

Sarcopenia and frailty are themselves associated with worsening critical illness outcomes, with a three-fold increase in mortality rate, reduced chance of discharge to their own home and a worse quality of life (Le Maguet et al, 2014). Older numerical age is an additional independent risk factor for post critical illness weakness and physical decline (Pfoh et al, 2016). Owing to the complex overlap between premorbid muscle mass, frailty and age, it is difficult to separate these as individual risk factors for critical illness muscle wasting. However, they each likely have a significant impact on patient recovery, and because of clinicians' inability to modify these during critical illness, these factors need to be recognised as potentially non-addressable in terms of recovery.

How do we prevent muscle wasting?

Despite the prevalence and impact of muscle wasting in critical care and over a decade of research, the majority of interventions have been shown to be ineffective.

Physical exercise in isolation

Many investigators hypothesised that intensive physical rehabilitation and resistance exercise may lead to increased muscle synthesis, therefore shifting these patients from an anti-anabolic to an anabolic state. This attitude remains prevalent among clinicians, patients and relatives.

However, studies have demonstrated no improvement in physical function or health-related outcomes in critically ill patients with physical rehabilitation alone (Denehy et al, 2013). This is despite the grade I evidence for physical rehabilitation in other disease states.

This lack of improvement is likely multifactorial in origin. One factor is the reduction in muscle protein synthetic ability in critical illness as a result of the associated systemic inflammatory state; inflammation has long been associated with more severe wasting (De Jonghe et al, 2002; Hodgson et al, 2015). Further, critically ill patients are unable to exercise sufficiently to stimulate an anabolic state, demonstrating a significantly lower exercise tolerance than healthy controls (Puthucheary and Denehy, 2015). Last most trials assume population homogeneity and, unsurprisingly, the presence of heterogeneity, eg chronic disease states, frailty and age, modifies patients' response to exercise (Puthucheary and Denehy, 2015).

Importantly, in health, resistance exercise with protein intake results in an increase in muscle protein synthesis (Moore et al, 2009) and therefore it would be logical that the same is true for patients in intensive care. To emphasise an earlier point, exercise without exogenous amino acids is catabolic. However, there have been no such trials of combined nutritional and exercise interventions completed to date, and the results of the NEXIS trial are awaited (NCT03021902).

Increased protein and calorie intake

In health, increased protein delivery stimulates muscle protein synthetic responses and provides amino acids that can be incorporated into new muscle (Atherton and Smith, 2012). This is being tested currently in the EFFORT (NCT03160547) and the HIGH WHEY (NCT02815527) trials. However, data to date suggest that protein delivery in isolation does not result in its availability for muscle use and does not reduce muscle wasting (Hermans et al, 2013). This is likely to be multi-factorial, as a result of the muscle full effect (a metabolic response by which muscle protein synthesis is no longer stimulated once a threshold ingestion of amino acids has been reached) (Atherton and Smith, 2012), inflammation (a major anti-anabolic stimulus) and a lack of energy for protein turnover (a highly energy-dependent process) (Puthucheary et al, 2018).

Studies focusing on increasing calorie delivery have not demonstrated improved outcomes. Instead, increasing calories increases adipose tissue accumulation, with no associated muscle preservation (Tian et al, 2015). This results in a relative decrease in lean muscle mass with no improvement in patient outcomes and a possible increase in mortality (Tian et al, 2015). A significant proportion of nasogastric feed calories are delivered in the form of lipid, and impaired beta oxidation would explain this pathophysiology, akin to propofol infusion syndrome (Mirrakhimov et al, 2015).

With both protein and calories in enteral feeds not being effective in maintaining muscle mass, the use of trophic feeding vs full feed in critically unwell patients was also investigated. This demonstrated no significant differences between groups in terms of ventilator-free days, infective complications or 60-day mortality (Rice et al, 2012).

So what does work?

No individual intervention, in isolation, can significantly reduce muscle wasting in critically unwell patients. A more holistic and pragmatic approach that is key to improving outcomes is early mobilisation.

Mobilisation and physical rehabilitation are two distinct entities that are repeatedly conflated. Physical rehabilitation is (in the main) the use of exercise or exercises to increase

physical performance, either strength or endurance, with a goal in clinical practise to increase functional independence and health-related quality of life. Mobilisation, on the other hand, is a holistic multifaced intervention involving movement, not necessarily against resistance. To mobilise a patient, issues with pain, sedation, sleep and delirium are addressed. Changes in posture affect lung perfusion and ventilation (Zafiropoulos et al, 2004) and mobilisation may improve gut function (Simrén, 2002). Finally, to mobilise one has to work against gravity, offering a small amount of resistance exercise. The summation of this is a minimisation of the anti-anabolic effects of critical care therapy immobilisation, a major driver of altered protein homeostasis. The benefits of mobilisation can be summarised as:

- Minimising complications of bed rest – such as pressure ulcers and venous thromboembolism
- Addressing the sequelae of intensive care unit-acquired weakness
- Promoting a reduction in sedation
- Possible improvement in delirium
- Promoting improved functional outcomes
- Improved patient mood and providing a feeling of accomplishment, in a situation where patients often feel they have little control (Denehy et al 2017).

It therefore appears that, while individual intervention strategies themselves do not improve outcomes, early patient mobilisation has a positive effect on almost all areas of patient care. Through this it may be possible to minimise subsequent disability in critical illness survivors (Denehy et al, 2017). It is also important to highlight that, when done correctly, early mobilisation is a safe and feasible intervention (Denehy et al, 2017).

In terms of functional outcomes, the benefits of mobilisation have long been established as regards to reductions in delirium, days of mechanical ventilation, critical care length of stay and an improved patient function at discharge (Schaller et al, 2016). Mobilisation is extremely difficult to deliver outside a holistic bundle. As a component of the ABCDEF bundle, the effects on mortality and length of stay have been demonstrated in service improvement settings (Marra et al, 2017).

So why are patients not being mobilised?

Despite the consensus opinion on the importance of mobilisation, the evidence suggests this is not being done (Hodgson et al, 2014, 2015). Even in centres with mobilisation champions, uptake is low, and even lower in intubated patients (Hodgson et al, 2015; Parry et al, 2018). The reasons are multi-factorial, with the same individual factors and recurring themes holding back progress.

The first of these themes is clinician's expectations, beliefs and education around mobilisation. While commonly acknowledging it to be an important aspect of patient care, the broad consensus among clinicians is that a greater level of formal training is required. Clinicians report that the majority of their knowledge on mobilisation is in fact learnt on the job, with little understanding of the evidence base that underpins it (Parry et al, 2017).

Another influential factor is the culture and environment of the unit. Mobilising critically ill patients, especially when mechanically ventilated, is a labour-intensive task. It requires extremely motivated medical, nursing and physiotherapy input, and a belief in its effectiveness. Only when a positive and proactive mobilisation culture is encouraged will a step forward in patient care be seen (Parry et al, 2017, 2018).

Finally, despite all the above contributing factors, the most significant barrier to mobilisation is the fear surrounding its safety. When done well with sufficiently trained teams and set protocols, mobilising critical care patients has been proven to be safe, and the fear surrounding it unjustified (Parry et al, 2017). In a study of 1449 critical care patients mobilised, <1% of these had minor adverse events, with no major adverse events. Of these patients 593 were mobilised with endotracheal tubes in situ with zero extubations (Hodgson et al, 2014, 2015). Numerous protocols on mobilisation have been developed, including expert consensus opinions and the National Institute of Health and Care Excellence (2017) guidelines, in order to create a safe and reproducible approach to each patient (Hodgson et al, 2014).

Key points

- Muscle wasting is the most common complication seen in critical illness.
- It results in increased mortality, morbidity and reduced quality of life.
- The only intervention associated with reducing the chronic effects of muscle wasting is early mobilisation.
- Despite this early mobilisation is rarely performed on critical care units worldwide.
- The key to achieving greater mobilisation is team education, emphasising its safety and promoting a positive mobilisation culture on critical care units.

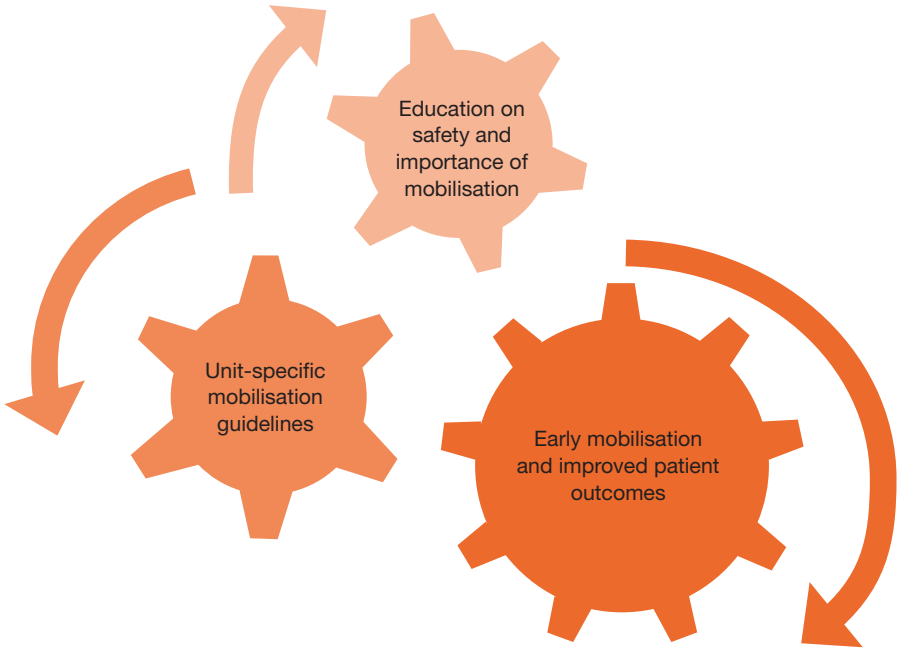

Figure 3. Encouraging early mobilisation.

In order to achieve more patient mobilisation, a shift needs to be made to change the culture and remove the fear surrounding it, with the emphasis being that each member of the team has a role to play (Figure 3).

This is not simply a 'physiotherapist' problem, it is vital that doctors and nurses appreciate the importance of early mobilisation, and work together to support all members of the team, and the patient, in doing so.

Conclusions

Muscle wasting is both a common and dangerous complication of critical illness. It results in increase morbidity, mortality and a reduction in quality in life. To date, no individual treatment strategy has been found to be successful in reducing its impact. The best intervention currently to improve patients' outcomes is early mobilisation, but across the world this is still not being done. To minimise the subsequent disability seen in critical illness survivors, the current culture and fear surrounding early mobilisation requires change. Mobilisation is safe, feasible and improves patient outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

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