Muscle Wasting in the Critically Ill Patient - What Can Be Done Now to Minimise Subsequent Disability

Key Words

Critical illness; Muscle Wasting; Intensive Care; Critical Care; Mobilisation; Rehabilitation

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 world wide
- The key to achieving greater mobilisation is team education, emphasizing its safety and promoting a positive mobilisation culture on critical care units

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 paper highlights the significant impact muscle wasting has on critically ill patients' outcomes, how we can reduce it, and where we may be able to look to in the future.

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, whilst 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 JTN 2010).

Attempts to quantify the magnitude of muscle loss seen have commonly looked at changes in size of the rectus femoris (RF) 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 RF cross-sectional area (CSA) may act as a surrogate indicator for muscle wasting and aid prognostication (Seymour et al. 2009). During critical illness an average of 12.5% decrease in muscle CSA is seen over the first week, progressing to 17.7% at 10 days (Puthucheary et al. 2013).

This muscle loss is most severe if patients with multi organ failure (-15.7% vs -3% in single organ at day 7), rising to 20.3% when 4 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 RF CSA and associated weakness in in ventilated patients at day 10 (Parry et al. 2015) and further research has demonstrated this in extra-corporeal membranous oxygenation (a 19% reduction in RF CSA at day 10) (Hayes et al. 2018) and in tetanus(

This rapid loss of muscle is the major driver of the umbrella syndrome of Intensive Care Unit Acquired Weakness (ICU-AW). Other components include critical illness myopathy (CIM), critical illness polyneuropathy (CIPN), and critical illness polyneuromyopathy (CIPNM). Whilst often referenced as separate entities, in clinical practice these are likely overlying pathologies and 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).

CIM is a primary symmetrical myopathy associated with predominantly proximal muscle weakness and associated muscle atrophy. In contrast, CIPN is a primary symmetrical neuropathy, with predominantly distal weakness, sensory loss and limited atrophy (Shepherd et al. 2017). CIPNM has been described as a combination of the CIM and CIPM, with both a symmetrical myopathy and neuropathy present. Similarly to CIM, CIPM too is characterised by primarily proximal weakness, however, as seen in CIPN, predominantly distal sensory loss is seen. In advanced stages, all three of these of pathologies are associated with reduced deep tendon reflexes, physical weakness, and prolonged mechanical ventilation (Stevens et al. 2009). Diagnostic testing is often challenging and unreliable, relying on a combination of electromyograms (EMG), nerve conduction studies (NCS), 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 EMG can be technically difficult in the critically ill patient (e.g. secondary to oedema). In the early stages of critical illness EMG/NCS findings are universally abnormal and unrelated to subsequent weakness (Coakley et al. 1993). CIPN is the most uncommon, but should be looked for in the setting of persistent disability, which these patients are at risk of (Latronico and Guarneri 2008). Of note, testing for non-excitable membrane may be the exception to this, in that in predicts the development of ICU-AW (Weber-Carstens et al. 2009). This technique remains one primarily used in research and the neurological components of ICU-AW 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 co-morbidities 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 3 times that of healthy working adults, and comparable to patients living with chronic diseases (Herridge et al. 2011). With only 27% of ICU services in the UK offering follow up service post hospital discharge (as advised by the National Institute of Health and Care Excellence), 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) (Fig. 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 (MPS) and muscle protein breakdown (MPB) 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 MPS is observed, surpassing MPB 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 MPS, relative to MPB, 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). This is not true of smaller animals such as rodents, where alteration in muscle protein breakdown is the major driver (Phillips et al. 2009).

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 (Brealey et al. 2002), dysregulated beta oxidation (Puthucheary et al. 2018), and impaired GLUT-4 translocation (Weber-Carstens et al. 2013) leads to a bioenergetics crisis and decreased intramuscular ATP content (Puthucheary et al. 2018). Current nutritional therapies are unable to address this as a result of both impaired glucose uptake and down-regulated 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 (Constantin et al. 2011; Puthucheary et al. 2018). Intramuscular inflammation (and hypoxic signalling) additionally impairs glucose metabolism by the Pasteur Effect (Fig 2.) (Puthucheary et al. 2018).

Who is at risk?

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

Critical illness specific risk factors

A broad range of studies have 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.

The use of the APACHE II score and the presence of systemic inflammatory response syndrome (SIRS) have also demonstrated this effect, with higher scores and the presence of SIRS correlating with increased risk of myopathy and neuropathy (De Letter et al. 2001; Hodgson and Tipping 2017). Biochemical and physiological markers such as raised serum C-Reactive Protein, low PaO_2/FiO_2 ratios and low serum bicarbonate have found similar associations (Puthucheary et al. 2013).

Contrary to earlier reports, the use of neuromuscular blockade agents are not associated with the development of ICU-AW (Puthucheary and Montgomery 2010; Papazian et al. 2010). These earlier case reports were confounded by high dose corticosteroid use, and sedation and ventilation practises not used in modern critical care. The only randomised controlled trial to test this showed no increased incidence of ICU-AW (Papazian et al. 2010) even with corticosteroids (Puthucheary and Montgomery 2010). NMBA use may even be beneficial, as a decrease in circulation inflammatory markers was noted (Forel et al. 2006; 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 3 fold increase in mortality rate, reduced chance of discharge to their own home and a worse quality of life. (Le Maguet et al. 2014; Bagshaw et al. 2015). Older numerical age is an additional independent risk factor for post critical illness weakness and physical decline (Pfoh et al. 2016). Due to the complex overlap between pre-morbid 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 due to our 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, multiple studies have demonstrated no improvement in physical function or health related outcomes in critically ill patients with physical rehabilitation alone (Denehy et al. 2013; Walsh et al. 2015; Moss et al. 2016). 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 due to the associated systemic inflammatory state; inflammation has long been associated with more severe wasting (Hodgson et al. 2015) add de Jonghe JAMA 2002. Further, critically ill patients are unable to exercise sufficiently to stimulate an anabolic state, demonstrating a significantly lower exercise tolerance than healthy controls

(Sommers et al. 2019). Lastly most trials assume population homogeneity, and unsurprisingly, the presence of heterogeniety e.g. chronic disease states, frailty and age are modifiers to patients response to exercise (Puthucheary and Denehy 2015; Sommers et al. 2019).

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 our patient population. 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 we await the results of the NEXIS trial (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 (Pitkänen et al. 2003). This is being tested currently in the EFFORT (NCT03160547) and TARGET PROTEIN (NCT02815527) trials. However data to date suggests 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 MPS is no longer stimulated once a threshold ingestion of amino acids has been reached) (Biolo et al. 1995; Atherton and Smith 2012), inflammation (a major anti-anabolic stimulus) (Vesali et al. 2010) and a lack of energy for protein turnover (a highly energy dependant 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; Deane et al. 2020 Jan 6). 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 of maintenance of 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). These findings remained true at 1 year follow up, with no improved physical function or mortality seen in either group (Needham et al. 2013).

So what does work?

No individual intervention, in isolation, has demonstrated an ability to 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/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 multi-faced 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 sores and venous thromboembolism
- Addressing the sequelae of ICU-AW
- 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, whilst individual intervention strategies themselves do not improve outcomes, early patient mobilisation has a positive effect on almost all areas of patient care. It is through this that we may be able minimise subsequent disability in critical illness survivors (Schweickert et al. 2009; 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, ICU length of stay and an improved patient function at discharge (Schweickert et al. 2009; Schaller et al. 2016). Mobilisation is extremely difficult to deliver outside a holistic bundle. As a component of the ABCDEF bundle (Ely 2017), the effects on mortality and length of stay have been demonstrated in service improvement settings (Marra et al. 2017; Chohan et al. 2018).

So why aren't we mobilising patients?

Despite the consensus opinion on the importance of mobilisation, the evidence suggests we are not doing this (Hodgson et al. 2014; Hodgson et al. 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. Whilst commonly acknowledging it to be an important aspect of patient care, the broad consensus amongst 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 pro-active mobilisation culture is encouraged, can we expect to see a step forward in patient care (Parry et al. 2017; Parry et al. 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. Five hundred and ninety three of these patients 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 Clinical Excellence guidelines, in order to create a safe and reproducible approach to each patient (Hodgson et al. 2014; NICE 2017).

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

Conclusion

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 our patients' outcomes is early mobilisation; however across the world this is still not being done.

If we want to minimise the subsequent disability seen in critical illness survivors, it is the current culture and fear surrounding early mobilisation that requires change. Mobilisation is safe feasible, and improves patient outcomes.

Figures

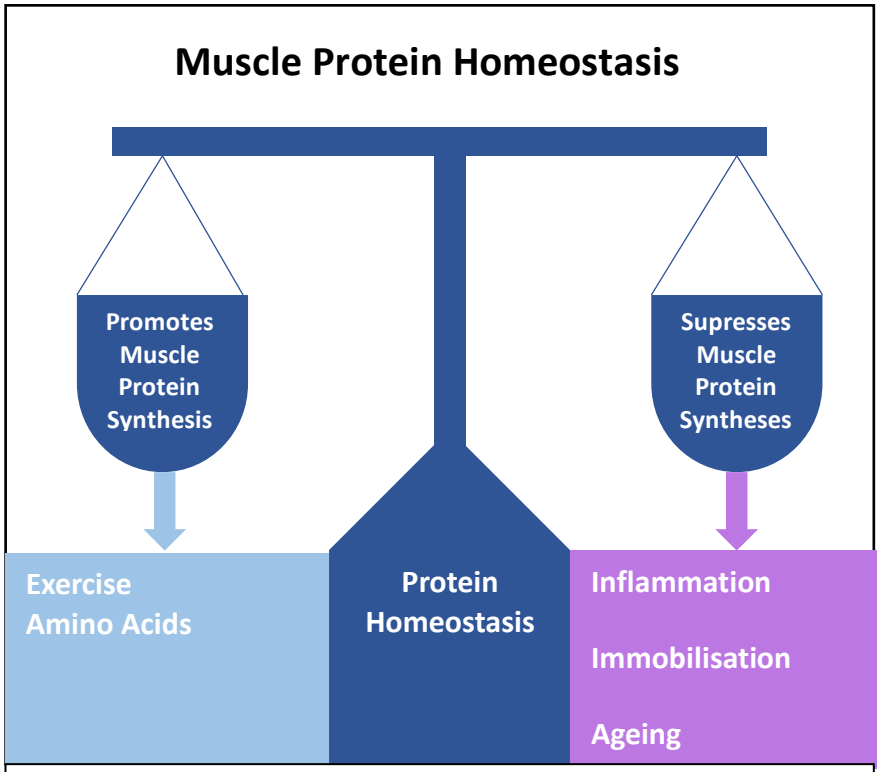

Fig 1. In health a fine balance between MPS and MPB is maintained. The presence of anabolic stimuli, such as exercise,or amino acids, will tilt this scale towards MPS (with insulin supressing MPB). The presence of anti-anabolic stimuli such as inflammation, immobilisation and advanced age will instead supress MPS.

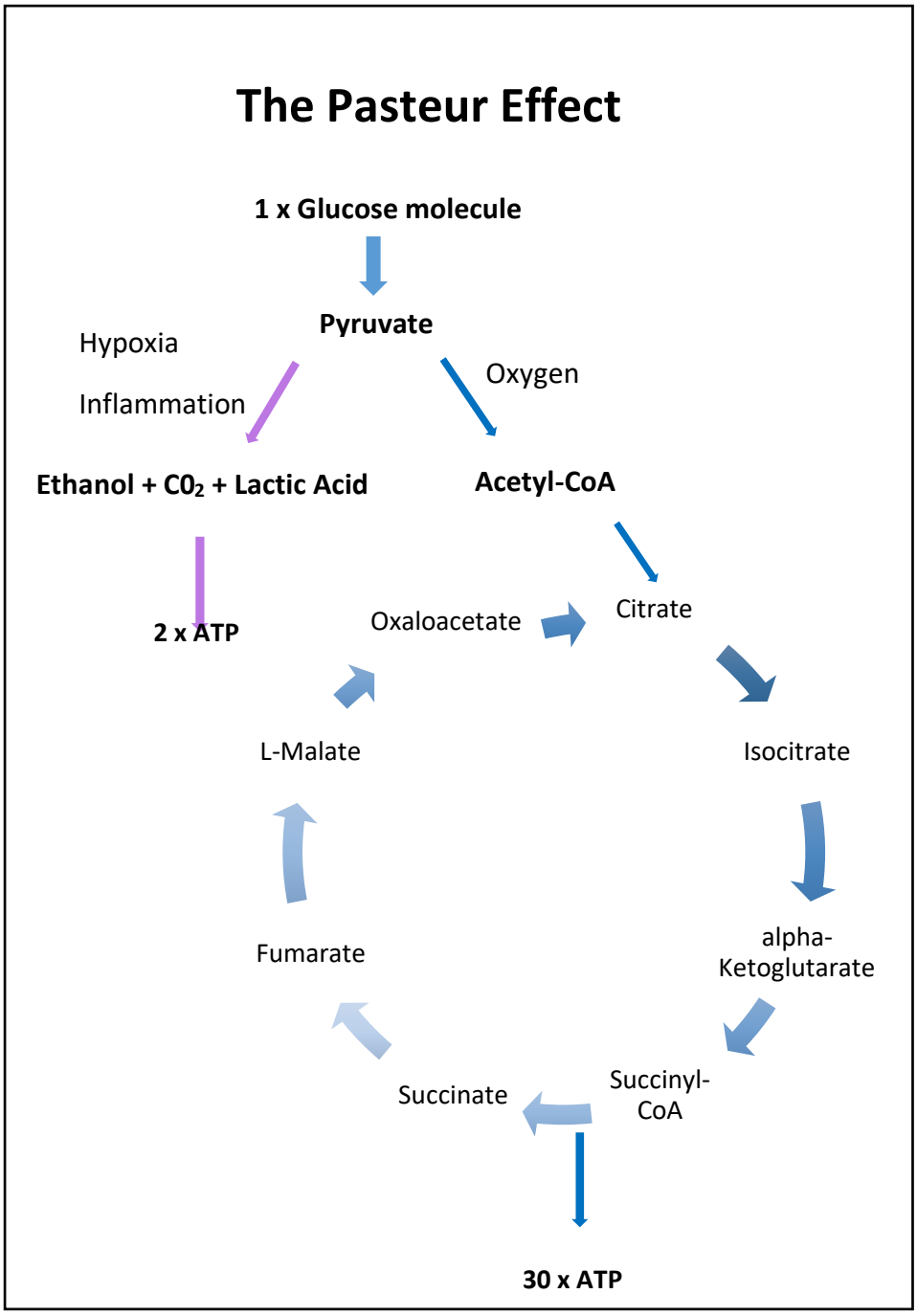

Fig 2. The Pasteur Effect refers to the inhibition of anaerobic metabolism with the presence of oxygen, resulting in improved efficiency of glucose metabolism. With the production of approximately 30 ATP molecules for every 1 glucose molecule. The presence of hypoxia or inflammation results in inhibition of Pyruvate Dehydrogenase Kinase, a less efficient system and the production of only 2 ATP molecules.

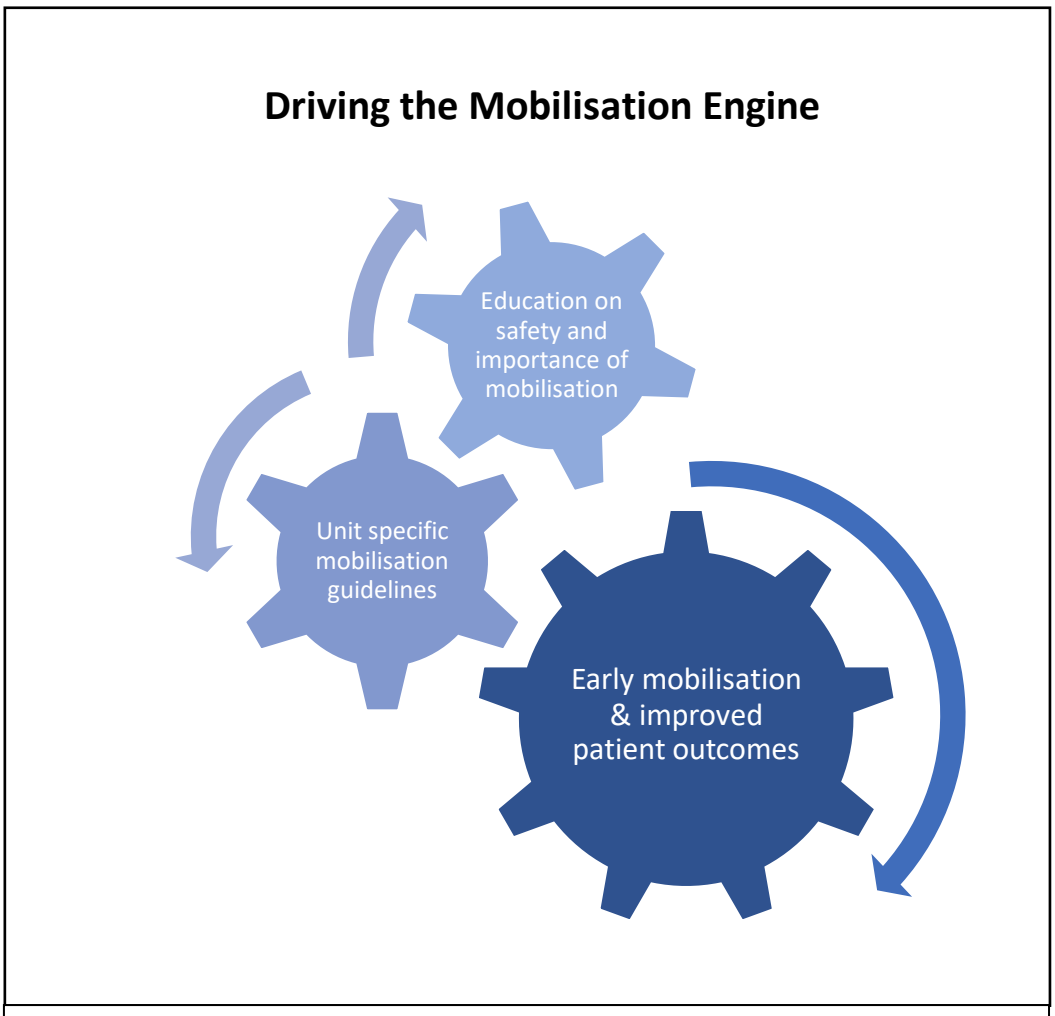

Figure 3. In order to successfully employ early mobilisation in critical care we need to ensure adequate education of its importance, emphasis on its safety and the distribution of protocols and guidelines.

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