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The Final Thesis

Preventing Intensive Care Unit Acquired Weakness: a Literature Review

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ABSTRACT

This thesis studies and presents strategies for preventing Intensive Care Unit Acquired Weakness in critically ill patients. This literature review aims to demonstrate standard practices for diagnosing muscle wasting and the up-to-date pathophysiology, divided into critical illness myopathy and critical illness neuropathy.

Concerning prevention, mobilization/ physiotherapy, electrical stimulation, nutrition, and pharmacological treatment are addressed separately.

This thesis concludes that prevention strategies focus on reducing the duration of Intensive Care Unit stays, early treatment of sepsis and infection, minimizing the use of neuromuscular blocking agents and sedatives, and ensuring adequate nutrition.

Mobilization and physiotherapy are vital in preventing muscle wasting. Early mobilization shows potential in reducing the incidence of Intensive Care Unit-Acquired Weakness and increasing lower limb strength. However, the effectiveness of early versus regular mobilization remains under debate. The development of standardized protocols for early mobilization and technological advances, such as robotics and virtual reality, could enhance physiotherapy and rehabilitation in the Intensive Care Unit.

While protein intake doesn’t seem to reduce the incidence of Intensive Care Unit Acquired Weakness, protein deficiency is common in Intensive Care Unit patients, and early enteral nutrition is recommended.

Pharmacological interventions, including proteolytic inhibitors and autophagy regulators, show promise in preserving muscle mass and function. Drugs such as eicosapentaenoic acid and heat shock protein 72 inducers also show protective effects against muscle atrophy and weakness. Intensive insulin therapy has the most promising preventative potential. The most important keywords to find accurate literature were ICUAW, ICUAW and Prevention, and the significant preventative measure.

KEYWORDS

Intensive Care Unit Acquired Weakness, ICUAW, ICUAW and Pathophysiology, ICUAW and Prevention, ICUAW and Mobilization, ICUAW and Physiotherapy, ICUAW and Nutrition, ICUAW and NMBAS, ICUAW and Pharmacological prevention, ICUAW and electrical stimulation, ICUAW and NMES, Muscle wasting.

INTRODUCTION

Intensive Care Unit Acquired Weakness (ICU-AW) is a challenge in critical care settings, slowing patient recovery and prolonging hospital stays. ICU-AW not only compromises physical function but also contributes to long-term morbidity and mortality among critically ill patients. It often leads to prolonged mechanical ventilation, delayed weaning, and increased dependency on intensive care interventions. ICU-AW can have diverse consequences for patients, extending even after their hospitalization. Furthermore, ICU-AW is associated with long-term functional impairment and diminished quality of life.

Intensive Care Unit Acquired Weakness is a component of Post-Intensive Care Syndrome (PICS), a constellation of physical, cognitive, and psychological impairments experienced by critical illness survivors. In addition to ICU-AW, which is one of the three main parts of PICS, another manifestation of PICS includes cognitive dysfunction, such as memory deficits, attention impairment and executive dysfunction. Lastly, Psychological dysfunction, such as anxiety, depression, and post-traumatic stress disorder (PTSD).

The review aims to explore diverse strategies for preventing Intensive Care Unit Acquired Weakness, highlighting the varied approaches and interventions available to healthcare professionals. The objectives to present these strategies include early mobilization, physiotherapy interventions, pharmacological treatments, nutritional therapies, and electrical stimulation. Through this literate search, the review has the goal to provide healthcare providers inspiration to manage ICU-AW better, ultimately improving patient outcomes and the quality of critical care delivery.

LITERATURE SELECTION STRATEGY

The medical databases PubMed, Clinical Key, Google Scholar, The New England Journal of Medicine, Society of Critical Care Medicine, and UpToDate were used to find accurate articles. The Keyword ICU-AW was used to obtain 8330 articles. The keyword prevention and significant preventative measures, such as Nutrition, were used to narrow down the search for necessary articles. After reading the abstract and title, 71 sources were selected that represent the newest insight into the pathophysiology and the most significant preventative measures.

The availability of free full text limited the search. Two figures have been used in this work. Figure 1 presents a potential algorithm that can be used to diagnose muscle wasting, and Figure 2 is a possible protocol that can be used in an Intensive Care Unit setting.

DEFINITION OF INTENSIVE CARE UNIT ACQUIRED WEAKNESS

Intensive Care Unit Acquired Weakness is a neuromuscular disorder characterized by generalized muscle weakness and paralysis or both that occurs in critically ill patients during their stay in the intensive care unit. This condition typically affects limb and respiratory muscles, leading to difficulties in mobility, weaning from mechanical ventilation, and overall physical function. ICU-AW can be divided into critical illness neuropathy and critical illness myopathy, while they can co-occur (1).

CLINICAL DESCRIPTION/ DIAGNOSIS

Intensive Care Unit Acquired Weakness, often referred to as muscle wasting, is comprised of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM), which differ in the underlying pathophysiology. If both CIP and CIM are present, it is called critical illness neuromyopathy (CINM) (2). Risk factors for developing muscle wasting include increased patient age, longer duration of Intensive Care Unit (ICU) stay, sepsis, systemic corticosteroids, female sex, and prolonged sedation (3)(4).

In general, the prevalence of ICU-AW fluctuates due to factors like patient demographics, risk factors, assessment timing, and diagnostic methods (4).

For example, 26 to 65% of patients who were mechanically ventilated for seven days already showed signs of weakness (4), while up to 67% of patients who were ventilated long term for more than ten days had weakness diagnosed (5).

Muscle wasting also affects the diaphragm: A 2014 systematic review found a median prevalence of 43% (IQR 25–75%) across 31 studies, with diaphragm dysfunction potentially being more common than limb muscle weakness (6).

Clinically, besides an overall reduction in muscle mass, muscle wasting after critical illness is presented by a flaccid and symmetrical weakness of the limbs, while proximal muscles are more affected than distal muscles. However, facial and ocular muscles show no signs of weakness. Therefore, hyporeflexia, as well as hypotonus of the muscles, is present (4).

Weakness prolongs the duration of mechanical ventilation and ICU stay, contributing to increased ICU mortality (7). The recovery potential of skeletal muscle varies significantly after the resolution of critical illness, with some survivors experiencing long-term weakness while others may achieve near-complete recovery. This highlights the importance of understanding and addressing weakness in critical care, as prolonged mechanical ventilation and ICU stays are associated with complications that can further slow the recovery process (8).

Besides that, especially the diaphragm and accessory respiratory muscles suffer atrophy, which causes consequent weakness and, therefore, prolonged ventilation. According to a cohort study from 2018, diaphragm atrophy occurred by more than 10% in 78% of patients already by day 4, and the decreasing diaphragm thickness was related to abnormally low inspiratory effort (9)(10).

The diagnosis of ICU-AW happens at the bedside of critically ill patients. Initially, the patient´s level of consciousness is assessed since the examination of muscle strength depends on it. There are several methods for cognitive assessment: GCS, the Richmond agitation-sedation score, and the Confusion assessment method. That is why the diagnosis of muscle strength can only be assessed without active sedation of the patient (11).

A commonly used tool for effectively assessing muscular strength is the Medical Research Council (MRC) Scale for Muscle Strength (12). It assesses the muscle strength of 6 muscle groups on a scale of 0 to 5. Bilaterally, shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors are assessed. Usually, an MRC score below 46 means ICU-AW is present (11).

Another possible, faster way to assess the patient's muscle strength is hand grip strength. However, according to Lee JJ et al., handgrip strength cannot reliably predict in-house mortality or the duration of mechanical ventilation compared to manual muscle testing (12).

If the cause of altered consciousness cannot be lifted, and active manual muscle testing cannot be performed as well as persistent muscle weakness is present, electrophysiological muscle testing can be performed, which can specify the mechanism of ICU-AW, differentiating CIP and CIM and, therefore, the functional outcome: According to Intiso et al., muscle weakness has a worse prognosis and slower recovery if the underlying cause is CIP instead of CIM (13).

Under the category of electrodiagnostic testing are nerve conduction studies, electromyography, and repetitive nerve stimulation.

The following figure, presented by Farhan et al., could be used as an algorithm to diagnose ICU-AW in an ICU setting (11):

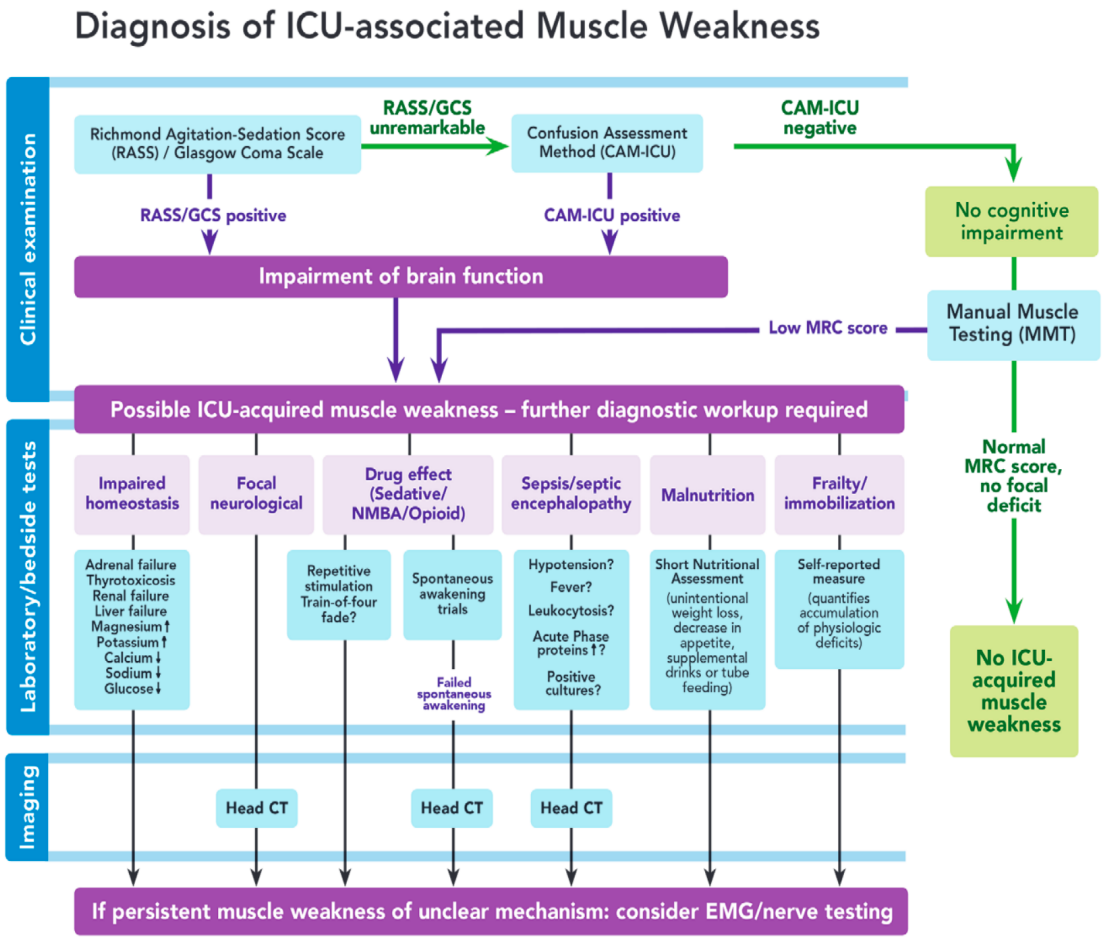

Fig. 1 Diagnosis of ICU- associated Muscle Weakness (11)

Lastly, muscle ultrasound can be used to evaluate the muscle itself by measuring its thickness and echogenicity. A 2018 study suggested that muscle ultrasound should be a routine part of diagnostics in an ICU setting for patients at risk of developing ICU-AW (14).

UNDERLYING PATHOLOGY OF ICUAW

As already mentioned, ICU-AW is comprised of two significant pathologies, critical illness myopathy, and critical illness polyneuropathy, while a combination of both is also possible.

According to Lacomis et al., in their study, 42% of their patients developed acute myopathy while only 13% developed acute axonal polyneuropathy. Hence, CIM can be seen as more common. However, the muscle functionality in both types is similar (15). In the following, several pathophysiological mechanisms for the development of CIM and CIP shall be presented.

Critical Illness Myopathy

Muscle necrosis and atrophy are myopathic changes in CIM (16)(17). Compared to myofibrillar breakdown, however, the main feature of muscle pathology in CIM is the breakdown of myosin and myosin-related proteins (18)(19). The cause of this specific pathology compared to other forms of muscle atrophy (e.g., muscle inactivity or corticosteroid therapy) is not fully understood. However, animal studies that mimic the ICU stay have been performed, suggesting that the absolute lack of muscle contraction resulting from deep sedation and ventilation causes this unique type of atrophy compared to other diseases (20).

Proteolysis/Autophagy/Caspases

Muscle wasting in critical illness results from an imbalance between protein or muscle breakdown (catabolism) and synthesis (anabolism), where in the early stages of critical illness, the degradation processes of the structural and contractile proteins are intensified (21). In critically ill patients, the body is undergoing massive stress (e.g., sepsis, immobilization, surgery). In order to survive, the body releases catecholamines, glucocorticoids (stress/ catabolic hormones), and pro-inflammatory cytokines. It activates the sympathetic nervous system, which triggers a shift to proteolysis and hinders protein synthesis (22).

One of the proteolytic pathways in CIM is the ubiquitin-proteasome system or UPS. During critical illness, this system is intensified by bedrest and the inability to utilize the muscle, as well as inflammation, oxidative and energy stress. Ubiquitin ligases are enzymes that target and mark proteins with ubiquitin components, so they are further degraded by proteasomes during proteolysis (4)(21). Different proteolytic enzymes, such as caspases and calpains, seem to play a role in the degradation of actinomyosin complexes, which reduce contractility (18)(23).

Interestingly, UPS plays a more significant role in the early phases of critical illness since its activity is reduced in the long term critically ill, suggesting that persisting muscle atrophy and weakness are caused by the inability of the muscle to regrow (24).

Autophagy is another factor leading to CIM. It is a physiological process where autophagosomes degrade larger cell structures. In a healthy body, autophagy is important for muscle homeostasis because it removes toxic cellular components. Hence, overactivation of autophagy causes muscle atrophy by proteolysis, and increased inhibition results in the buildup of toxins and damaged cell components, which also causes atrophy. Therefore, it is believed to be dysregulated in critical illness (25).

However, similar to the UPS, dysregulated autophagy could not be proven in patients with muscle wasting present six months after ICU stay (24). Interestingly, according to Auclair et al., the ubiquitin pathway is triggered by the continuous injection of corticosteroids in a rat model study, suggesting the induction of muscular atrophy (26).

As mentioned, in contrast to early critical illness stages with heightened proteolysis, the molecular regulation of sustained muscle wasting in long-term survivors is not well-explored. According to Dos Santos et al., skeletal muscle UPS and autophagy networks normalized six months post-ICU discharge (24). Rather than continued proteolytic-mediated muscle loss, muscle mass recovery was impaired. Another study identified reduced myogenic stem cells in persistently atrophic muscles, indicating impaired muscle regeneration in sustained ICU-acquired weakness. In a pre-clinical sepsis model, satellite cell depletion led to lasting weakness three months after sepsis resolution caused by increased apoptosis (27).

Mitochondrial dysfunction

Mitochondria supply the cell with ATP by oxidative phosphorylation to meet its energy demand. It is already well-established that during CIM, mitochondrial dysfunction is present, proven by muscle biopsies showing decreased activity of cytochrome c oxidase, succinate dehydrogenase and other enzymes relevant for cellular respiration (23)(28). Furthermore, according to Dos Santos et al., the mitochondrial concentration in critically ill patients is also lowered and normalized after six months (24). The ATP concentration itself is proven to be reduced in skeletal muscles (29). In conclusion, the cellular energy demand is not met during CIM, facilitating muscle atrophy.

Systemic Inflammation

A systematic review with meta-analysis from 2020 presented that a decrease in skeletal muscle strength and mass is linked to higher levels of inflammatory markers circulating in the blood (30).

Tumor necrosis factor-alpha (TNFα), interleukin 1, and interleukin 6 are proven to be key players in the pathophysiology of muscle atrophy and weakness during critical illness (28). For example, the tumor necrosis factor causes upregulation of the UPS and, therefore, enhances muscle degradation (31). Overall, systemic inflammation, marked by cytokine elevation, seems to play a role in skeletal muscle atrophy during critical illness, including sepsis and COVID-19 infection. This systemic inflammation is notably higher in patients who develop ICU-acquired weakness (28).

Critical illness polyneuropathy

The exact pathophysiology of axonal injury is still under investigation. The following paragraph presents ideas of mechanisms causing critical illness polyneuropathy (CIP).

In critical illness polyneuropathy, myelin sheaths are not damaged because it is a distal axonal sensory-motor polyneuropathy. For that reason, nerve conduction is usually normal or minimally reduced. However, the amplitude of compound muscle action potentials and sensory nerve action potentials are reduced or not stimulable (32).

One might suggest that microcirculatory insufficiency, caused by systemic inflammation, including cytokines and reactive oxygen species, causes anaerobic metabolism and, therefore, distal nerve ischemia and breakdown (32).

Additionally, Fenzi et al. found out that endothelial cells are activated by the overexpression of E-selectin in microvessels within the endoneurium of peripheral nerves during sepsis, possibly contributing to axonal degradation (33).

Another important risk factor for the development of CIP is hyperglycemia in critical illness. Hyperglycemia poses a significant risk for critical illness polyneuropathy as nerves uptake glucose via the insulin-independent GLUT3 transporter, rendering them susceptible to high glucose levels. Elevated glucose levels directly result in reactive oxygen species production, potentially harming nerves. Furthermore, hyperglycemia triggers pathways linked to cell damage, such as advanced glycation end-product production in endothelial cells. These endproducts contribute to basement membrane hypertrophy, disrupting the blood-nerve barrier, which could change the nerve environment and, therefore, damage the nerve (21).

Another possible pathophysiological factor is channelopathy. Action potentials travel along the nerves by sodium and potassium ion channels. Any change in sodium or potassium concentration

or mentioned channels might diminish action potential transmission and cause nerve dysfunction. According to Koch et al., inactivation of sodium ion channels is a primary cause of CIP. Also, they indicate that illness severity corresponds to abnormal depolarization (34).

PREVENTION

In general, for obvious reasons, the most effective preventive strategy for the development of ICU-AW is to shorten the stay in the intensive care unit. That includes avoiding prolonged mechanical ventilation and immobilization by early and aggressive treatment of sepsis and infection, avoiding unnecessary usage of neuromuscular blocking agents and sedatives, and inadequate nutrition (35). Aggressive treatment of sepsis is one of the most important regiments in preventing ICU-AW since systemic inflammation is believed to be one of the main pathophysiological factors leading to loss of muscle mass (5).

Focusing on neuromuscular blocking agents (NMBAs), several case reports present their contributing effect on ICU-AW, especially in combination with corticosteroids (36). Since then, the clinical use of NMBAs has been reduced (37). However, according to Friedrich et al., numerous studies do not show negative effects, while some present neuromuscular degenerative effects consistent with NMBAs (18). According to Papazian et al., patients with severe acute respiratory distress syndrome (ARDS) even benefited from early administration of NMBAs, which resulted in more time off the ventilator without increased muscle weakness (38). A possible cause of the new differing data is newer treatment regimens and improved ventilation techniques in modern ICU settings (39). In conclusion, the association of NMBAs and the development of ICUAW remains uncertain and requires further research.

Another avoidable factor in the ICU setting is the use of glucocorticoids. Studies have shown their negative effect on muscle mass (40). For that reason, accurate dosing of glucocorticoids is likely indicated.

Additionally, communication and collaboration among healthcare teams are essential to ensure patient mobilization and an awareness of the patient's status to avoid unnecessary prolongation of the treatment in the intensive care unit, which results in a higher chance of developing ICU-AW (41).

Mobilization/Physiotherapy

Mobilization and physiotherapy are the most established practices already used in the ICU setting to prevent and decrease the severity of muscle wasting in the ICU. Several studies prove that especially early mobilization lowers the incidence of ICU-AW and, therefore, shortens the duration of the ICU stay (42 - 45). A recent study from 2023 revealed the effect of in-bed cycling on patients diagnosed with ICU-AW. It showed that in-bed cycling, together with an early mobilization protocol, reduced the incidence of ICU-AW at discharge and increased lower limb strength (46). For obvious reasons, this exercise can only be undertaken with neither sedated nor ventilated patients. Additionally, it has been shown to increase muscle strength solely in the lower limbs (46). It is important to mention that studies exist that deny that early mobilization, compared to regular mobilization, has any beneficial effect. In fact, according to Hodgson et al., early mobilization was associated with more adverse events, such as cardiac arrhythmia, altered blood pressure, and oxygen desaturation. This indicates that early mobilization if performed clinically, requires medical expertise in order to avoid patient harm (47). In addition, trials have been conducted that compared usual physical therapy to intensive and ICU-based physical therapy, revealing no improvement in physical strength and no decrease in the hospital length of stay (48–50). A systematic review and meta-analysis from 2021 confirmed that early mobilization shows a potential benefit for the development and severity of ICU-AW compared to late mobilization. Mainly, this study included a comparison between standardized versus systematic early mobilization, which is performed in a clearly defined protocol yet has no significant advantage over standard early mobilization (51).

Research in this area has its limitations. For example, mechanically ventilated patients can only be passively mobilized. No large randomized controlled trials exist. Specific knowledge gaps exist, such as a standardized protocol, for early mobilization (52).

However, a study from 2020 from the University of Minnesota addressed this problem by trying to develop and implement a protocol for early mobilization in the ICU (53):

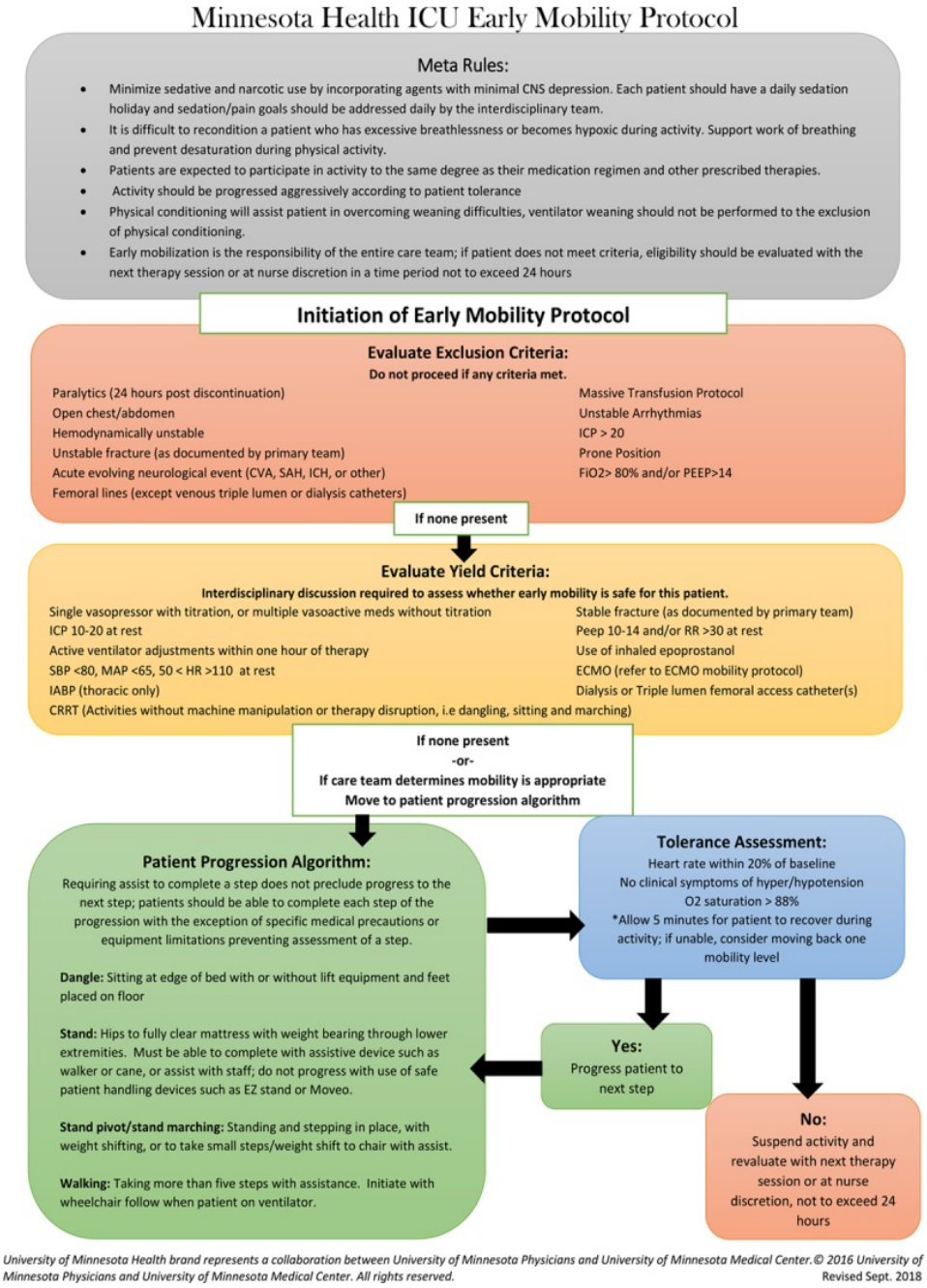

Fig. 3 Minnesota Health ICU Early Mobility Protocol (53)

According to their findings, implementing such a protocol proved to be successful in their adult ICU and increased patient mobilization since the staff was secure and comfortable. Communication was essential in this project, and no additional staff had to be implemented (53). Using such a standardized and detailed early mobilization protocol is promising since it erases insecurities among staff and helps to evaluate the effectiveness of further research.

Considering the advances in technology in physiotherapy in the ICU setting, a case report by Chillura et al. presented the usage of robotics and virtual reality assisting physiotherapy. In this case report, a patient was suffering from ICU-AW and had been in standard rehabilitation for two months without satisfying results. After treatment using robotics and VR, he was able to stand and walk with double support (54).

Further research needs to be undertaken to support the effectiveness of these methods. However, technological advances seem promising not only in physiotherapy and the prevention of ICU-AW but also in terms of rehabilitation in the ICU in general (55).

Neuromuscular Electrical Stimulation

Neuromuscular Electrical Stimulation (NMES) is a process in which a low-frequency electrical current of 30 – 50Hz stimulates targeted muscle groups with electrodes. The theory is that fast twitching and contractions cause functional repair and slow the process of muscle degeneration (56). A pilot study from 2010 already presented the promising effects of this type of treatment on muscle thickness (57). A newer study from 2023 compared NMES, range of motion exercises, and a combination of both, presenting that daily sessions preserved muscle strength and prevented ICU-AW. This leads to a decreased time of mechanical ventilation and ICU stay (44). In a meta-analysis from 2020, this result is confirmed by comparing 11 articles where routine NMES was performed in an ICU setting (56).

However, according to Maffiuletti et al., inconclusive evidence exists regarding the effectiveness of NMES in preserving muscle mass among ICU patients, likely due to a lack of patient stratification based on diagnosis and severity. For that reason, further research is needed to assess the long-term effects of NMES therapy on physical function and quality of life in ICU survivors, determine optimal dosages for preventing ICU-AW, and evaluate the feasibility, safety, and cost-effectiveness of NMES (58).

Nutrition

As already established, critical illness triggers a catabolic state, leading to muscle wasting and sarcopenia due to an imbalance in protein synthesis and breakdown (21). In ICU patients, the impact of poor nutrition is exacerbated by the added stress of inflammation, hormonal changes, and immobility. Malnutrition has been shown to contribute to complications such as infections

(59). Furthermore, a study from 2023 revealed a high incidence of ICU-AW in patients receiving enteral nutrition. Besides the general overfeeding of most critically ill patients, a correlation to the development of ICU-AW could not be proven.

Additionally, protein intake did not show any advantage for the incidence of ICU-AW; however, protein deficiency was profound in most ICU patients (60). According to Hermans et al., intensive feeding cannot protect against the lack of protein. Interestingly, comparing late versus early parenteral feeding to one another brought the result that a macronutrient deficit in the early stages of critical disease led to an accelerated recovery, meaning late parenteral feeding was beneficial. Also, the autophagosome formation was lower in patients receiving late parenteral nutrition (61). According to Fivez et al., parental feeding should be given as late as possible because it is bound to a higher incidence of complications such as infections, longer dependency on the ventilator, et cetera (62).

However, the consensus is that malnutrition is a detrimental risk factor, and enteral nutrition should be given early (63).

Pharmacological treatment

Since proteolysis and autophagy are two key drivers of ICU-AW, one might suggest that proteolytic inhibitors and autophagy regulators serve as potential preventative measures during the ICU stay.

For example, Bortezomib (Velcade) is a proteasome inhibitor, which is usually used in treating multiple myeloma and mantle cell lymphoma. A study from 2006 shows a preservation of muscle mass and a preservation of typical cellular structure in denervated rats (64). Additionally, a study from 2012 shows that the administration of bortezomib offers protection against ventilation-induced diaphragm contractile weakness, yet without prevention of atrophy (65). Since bortezomib has a narrow therapeutic range, and it is important to outweigh the toxicity against the therapeutic benefit, further research to find a UPS inhibitor that targets skeletal muscle specifically might be promising (66).

Similar benefits could result from the development of autophagy regulators. According to Levine et al., especially autophagy-inducing drugs promise potent treatments across various clinical diseases. They could also provide more insight into the physiology and pathophysiology of autophagy itself (67).

Research from 2010 reported about another proteolytic inhibitor: eicosapentaenoic acid. It inhibits the activation of caspases as well as the proteasomal pathway and has an antioxidant effect. On the one hand, this study proved that sepsis caused by endotoxins leads to a reduction in diaphragm function. On the other hand, it revealed that eicosapentaenoic acid protects against diaphragm atrophy and dysfunction by inhibiting calpain activation, suggesting a potential benefit for intensive care patients (68). A preclinical animal study revealed the protective role of heat shock protein 72 in the development of ICU-AW, specifically ventilator-induced diaphragm weakness. According to that study, pharmacologically induced overexpression of HSP72 by so-called BGP-15 protects the diaphragm from weakness, making it a potential therapeutic target (69).

Another possible therapeutic approach during critical illness is intensive insulin therapy. As mentioned, hyperglycemia, in general, leads to higher mortality and morbidity during critical illness (70). A study from 2006 revealed the impact of intensive insulin therapy on the reduction of incidence of CIM and CIP in surgical ICU- patients who were mechanically ventilated for more than seven days, subsequently reducing the incidence of prolonged mechanical ventilation (71).

Interestingly, this study also questions the effect of corticosteroids on CIM/CIP. Before, corticosteroids have been mentioned as a general risk factor for the development of muscle atrophy due to their catabolic effect (40). However, according to their findings, Hermans et al. suggest that corticosteroids do not worsen CIM and CIP when glycemic levels are regulated by insulin and kept in normal range, suggesting a protective effect due to their anti-inflammatory effect (71).

However, a newer meta-analysis from 2018 has again shown a strong association between the use of corticosteroids and the development of ICU-AW, suggesting that administration should be limited (72). A rat model study from 2023 revealed that insulin resistance is induced by immobilization and inflammation. The study confirms the importance of protein kinase b (Akt) and phosphorylated protein kinase b (pAkt) in the pathophysiology of insulin resistance, yet stresses that further investigation is needed. Also, this study highlights the role of Glycogensynthase-kinase-3-beta (GSK) and its effect on low muscle glycogen content in critically ill patients, explaining why ICU-AW does not solely rely on muscle atrophy (73). Due to the possible increase in insulin resistance in critical illness, further research in humans might be indicated, and intensive insulin therapy as a potential preventive measure for the decrease of the severity of ICU-AW is highlighted.

CONCLUSIONS/ RECOMMENDATIONS

In conclusion, the prevention of Intensive Care Unit Acquired Weakness primarily involves reducing the duration of Intensive Care Unit stay. This can be achieved through early treatment of sepsis and infection, minimizing the use of neuromuscular blocking agents and sedatives, and ensuring adequate nutrition. The role of neuromuscular blocking agents and glucocorticoids in Intensive Care Unit Acquired Weakness is still uncertain and needs further research. Effective communication among healthcare teams is also crucial to prevent unnecessary prolongation of Intensive Care Unit treatment.

Mobilization and physiotherapy are established practices in the Intensive Care Unit to prevent and decrease the severity of muscle wasting. Early mobilization, including in-bed cycling, has been shown to reduce the incidence of Intensive Care Unit Acquired Weakness and increase lower limb strength. However, early mobilization can be associated with adverse events and requires medical expertise. The effectiveness of early versus regular/late mobilization is still under debate, with some studies showing no significant advantage.

The development and implementation of standardized protocols for early mobilization, such as the example developed by the University of Minnesota, can be beneficial in increasing patient mobilization and erasing insecurities among staff.

Advances in technology, such as robotics and virtual reality, show promise in assisting physiotherapy and rehabilitation in the Intensive Care Unit. However, further research is needed to support their effectiveness.

Despite the high incidence of Intensive Care Unit Acquired Weakness in patients receiving enteral nutrition, there’s no proven correlation between overfeeding and the development of Intensive Care Unit Acquired Weakness. Protein intake doesn’t seem to reduce the incidence of Intensive Care Unit Acquired Weakness, but protein deficiency is common in Intensive Care Unit patients. Intensive feeding can’t compensate for protein deficiency, and supplementing enteral feeding with parenteral feeding doesn’t prevent atrophy but may increase muscle weakness. Parenteral feeding is associated with a higher incidence of complications and should be initiated as late as possible. However, the consensus is that malnutrition is a significant risk factor, and early enteral nutrition is recommended.

Pharmacological interventions present promising avenues for preventing Intensive Care Unit-Acquired Weakness. Proteolytic inhibitors like Bortezomib and autophagy regulators offer the

potential to preserve muscle mass and function. Additionally, compounds such as eicosapentaenoic acid and heat shock protein 72 inducers show protective effects against muscle atrophy and weakness. Intensive insulin therapy also emerges as a potential preventive measure. However, the impact of corticosteroids remains controversial. Further research is needed to fully understand these interventions' mechanisms and their potential to mitigate the severity of Intensive Care Unit Acquired Weakness in critically ill patients.

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