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Review

ICU-Acquired Weakness: From Pathophysiology to Management in Critical Care

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Abstract: Intensive Care Unit-Acquired Weakness (ICU-AW) is a common and severe complication in critically ill patients, characterized by profound and often prolonged muscle weakness. The complexity of its diagnosis and management requires a multidimensional approach that integrates clinical, electrophysiological, and imaging tools. This review focuses on the challenges in diagnosing ICU-AW, emphasizing the limitations of traditional methods such as manual muscle testing and electrophysiological studies, and highlights the emerging role of neuromuscular ultrasound (NMUS) as a promising, non-invasive diagnostic aid. Despite its utility, no gold standard exists for NMUS, making it an evolving area of research. The pathophysiological basis of ICU-AW involves multiple mechanisms, including critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and muscle atrophy due to disuse. Understanding these underlying mechanisms is crucial for advancing diagnostic strategies and informing therapeutic interventions. Recent insights into the molecular and cellular pathways involved, such as the role of oxidative stress, mitochondrial dysfunction, and the ubiquitin-proteasome system, have opened new avenues for targeted therapies. Management of ICU-AW remains challenging as no specific treatment has been proven fully effective. Current strategies focus on early mobilization, minimizing sedation, and optimizing nutritional support. Emerging therapies targeting molecular pathways involved in muscle degradation are under investigation, highlighting the potential to translate pathophysiological understanding into therapeutic innovations. This review underscores the need for ongoing research to establish standardized diagnostic protocols and develop targeted treatments for ICU-AW.

Keywords: intensive care unit-acquired weakness; ICU-AW; critical illness polyneuropathy; CIP; critical illness myopathy; CIM; sarcopenia; muscle degradation

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1. Introduction

Intensive Care Unit-Acquired Weakness (ICU-AW) is a medium- and long-term complication in critically ill patients that affects quality of life by increasing morbidity and healthcare costs [1]. Approximately 20 million people worldwide require admission to intensive care units (ICUs) each year. Within this cohort, the incidence of ICU-AW) is estimated to be around 25–30%, translating to an average of 3–6 million affected patients

annually. The incidence is even higher in surgical ICUs, where certain studies report rates ranging between 50% and 70% [2]. It represents a clinically relevant muscle weakness that appears in patients with critical illness and has no underlying cause other than the critical illness itself. It is characterized by symmetrical and predominantly proximal limb weakness with typical sparing of facial muscles and overall reduction in osteo-tendon reflexes. Respiratory muscles can also be affected [3]. Depending on the presence of neuropathy or myopathy, a distinction can be made between critical illness polyneuropathy (CIP), characterized by axonal damage identified through electrophysiological methods; critical illness myopathy (CIM), characterized by visible muscle damage on biopsy or electrophysiology; and finally, critical illness neuromyopathy (CINM), which involves elements of both neuropathy and myopathy [4]. The prevalence of ICU-AW in critically ill patients can reach 50%, with up to 2% of muscle mass lost daily [5]. The significance of ICU-AW for a patients' quality of life became particularly evident during the COVID-19 pandemic, as muscle dysfunction and reduced mobility were not only more prevalent in patients hospitalized in intensive care units for COVID-19, but could also persist up to six months after discharge [6,7]. Furthermore, ICU-AW significantly increases the mortality of patients admitted to the ICU. Although the precise cause in these patients is difficult to determine, most die from irreversible septic shock [8]. While the exact pathogenesis remains unclear, it is now evident that critical illness, the duration of stay in the intensive care unit, and the devices and therapies used in this setting serve as triggers for a wide range of cellular alterations that compromise nerve and muscle integrity [5].

2. Risk Factors

It is useful to classify the risk factors for ICU-AW into modifiable and non-modifiable, as shown in Table 1 [9].

Table 1. Risk factors for ICU-AW.

Modifiable	Non Modifiable
Hyperglycaemia	Premorbid health status
Drugs	Multiple Organ Failure
Parenteral nutrition	Sepsis and septic shock
Immobilization	Mechanical ventilation
	High lactate level

Abbreviations. ICU-AW = Intensive Care Unit-Acquired Weakness.

2.1. Premorbid Health Status

The premorbid functional state certainly influences the development of ICU-AW in different ways and for different reasons. The risk of developing ICU-AW is higher in older patients: studies show that the incidence of ICU-AW increases with age [10]. There is no unanimous consensus among studies regarding gender. While some identify female sex as an independent risk factor [11,12], others have found no statistically significant differences in the development of ICU-AW between the sexes [10,13]. The frailty of elderly patients prolongs their stay in the ICU and increases the severity of diseases and their mortality. It is also closely related to the development of sarcopenia, which further exacerbates this spiral of complications [14]. At the same time, obesity appears to be protective against the development of weakness in critically ill patients by reducing muscle mass loss through increased metabolism of fatty acids and glycerol [15].

2.2. Multiple Organ Failure

Multiple organ failure (MOF) has long been considered a crucial risk factor for the development of ICU-AW. It is characterized by sequential failure of two or more organs

and, in most ICU patients, is caused by a septic state. Although sepsis is the most frequent cause of MOF, muscle weakness also occurs as a complication of MOF caused by other conditions, such as acute pancreatitis, trauma, and cardiac arrest [2]. It is now established that also the severity of the underlying pathology predisposes patients to the development of neuromyopathy. The Acute Physiology and Chronic Health Evaluation (APACHE II) score as well as the Sequential Organ Failure Assessment (SOFA) score are higher in patients who will develop various forms of ICU-AW [10,16]. ICU-AW and MOF seem to exacerbate each other. Multiple organ failure is also the predominant cause of death in ICU-AW patients: a 2020 study showed that MOF caused by irreversible shock was the most common cause of death in this cohort. In most cases, it was septic shock; only in a minority of cases, it was hypovolemic shock [8].

2.3. Sepsis and Septic Shock

Sepsis, a systemic syndrome characterized by organ damage in the presence of an infection, is a major public health problem, leading to death in up to one third of affected patients [17]. It is one of the main causes of ICU admissions across all age groups: some statistics estimate that up to 50% of septic patients require intensive care [18]. The course of patients with sepsis is sometimes complicated by reduced muscle mass and, for those admitted to the ICU, by ICU-AW. Since sepsis coexists with many other clinical conditions, determining its role in the development of ICU-AW is challenging. Certainly, septic patients may present nearly all risk factors for ICU-AW described in this article. Additionally, sepsis activates specific mechanisms: studies in cellular, animal, and human models have shown that the main cause of muscle loss during sepsis is an imbalance between increased protein degradation and decreased synthesis of new muscle proteins [19].

2.4. Immobilization

In hospitalized patients, particularly the elderly, sarcopenia is not uncommon. Muscle atrophy can develop acutely due to reduced muscle use following an illness, or chronically as part of the aging process [20]. Immobilization is a well-established risk factor for the development of ICU-AW [2,3,14,21]. A 2014 study on patients following acute lung injury highlighted reduced mobility during hospitalization as a significant risk factor for persistent muscle weakness 24 months after the acute event [22]. Prolonged stays in intensive care units further increase the risk, as reduced mobilization is compounded by other factors such as infections, potentially muscle-toxic medications, mechanical ventilation, and more [10].

2.5. Mechanical Ventilation

Mechanical ventilation is one of the main risk factors for ICU-AW in the intensive care setting [23–25]. The risk of developing this form of muscle atrophy increases with the duration of mechanical ventilation, although some studies suggest that even a few hours of ventilation can act as a trigger for the process. The mechanism linking ICU length of stay, duration of mechanical ventilation, and the onset of ICU-AW is complex and not yet fully understood, as multiple factors are likely involved, including immobilization, the use of sedatives and muscle relaxants, malnutrition, and hypoxia [26,27]. Prolonged mechanical ventilation has also been associated with diaphragmatic weakness and atrophy, which further complicate the process of weaning from ventilation [28].

2.6. Glycemic Control

Several studies have shown that poor glycaemic control during the acute phase of illness is associated with the development of polyneuropathy and muscle weakness [11,29] and appears to worsen the prognosis of ICU patients [30]. Various mechanisms have been proposed to explain this phenomenon: hyperglycaemia seems to alter neuronal excitability,

has toxic effects on neurons, and may impair nerve microcirculation [27]. For these reasons, maintaining good blood glucose control, through insulin therapy and non-pharmacological approaches such as early mobilization, improves outcomes and reduces the incidence of ICU -AW [30,31].

2.7. Drugs

2.7.1. Neuromuscular Blocking Agents

The correlation between the use of neuromuscular blocking agents (NMBA) and the development of ICU-acquired weakness (ICU-AW) has been studied for a long time. Traditionally, NMBA use is considered a risk factor for ICU-AW [3,7,27], although the supporting data are inconsistent and do not provide a definitive answer. A 2016 meta-analysis of 2254 patients found only a modest association between NMBA use and acquired neuromuscular dysfunction, but the analysis was significantly biased due to the inclusion of studies on critically ill or septic shock patients [32]. A more recent 2023 meta-analysis suggested a potential association between NMBA use and ICU-AW, although it concluded that the available evidence remains weak, as it is primarily based on heterogeneous observational studies [33]. An older multicentred study on patients with severe acute respiratory distress syndrome (ARDS) demonstrated that NMBA use improved mortality rates without increasing the risk of muscle weakness [34]. The challenge in finding definitive studies on this topic lies in the difficulty of isolating the contribution of NMBA use to the development of ICU-AW from that of other risk factors, which are often present in the studied populations [35].

2.7.2. Glucocorticoids

Although glucocorticoids are associated with an increased risk of myopathy due to enhanced muscle catabolism [36,37], their role in the development of neuromyopathy in the context of ICU-acquired weakness remains unclear and controversial. Some studies suggest they may act as an independent risk factor [11]. A 2018 meta-analysis found a strong correlation between glucocorticoid use and ICU-AW, recommending careful consideration of their use [38]. However, other studies, particularly those examining low steroid doses, do not confirm this association [39]. Given that corticosteroids are a key component in the treatment of ARDS and septic shock, this discrepancy may be explained by the benefits of steroids, particularly in controlling systemic inflammation, which is pathologically linked to ICU-AW, and in reducing the duration of mechanical ventilation. According to some authors, these benefits may outweigh the potential and uncertain negative effects on neuromuscular integrity [40,41].

2.8. High Lactate Level

Serum lactate concentrations, long studied in sepsis and septic shock, are a crucial biomarker in critically ill patients. As an indicator of peripheral hypoperfusion, it is not only the absolute lactate value but also the kinetics of blood lactate levels that are indicative of prognosis and response to therapy [42]. A 2021 observational study conducted on a cohort of 68 patients demonstrated that hyperlactatemia (lactate level > 2 mmol/L) is an independent risk factor for the development of ICU-acquired weakness (ICU-AW) in critically ill patients [43].

2.9. Parenteral Nutrition

Proper nutritional support is essential for the prevention of ICU-acquired weakness (ICU-AW) in critically ill patients. Specifically, prolonged and early parenteral nutrition, by exacerbating multi-organ dysfunction and prolonging the length of stay in intensive care settings, increases the risk of ICU-AW [44].

3. Pathophysiology

The pathophysiology of ICU-AW is multifactorial, involving a combination of systemic inflammation, bioenergetic failure, oxidative stress, and microvascular changes, all contributing to both muscle and nerve dysfunction. The key factor in the pathogenesis is an imbalance between protein synthesis and muscle protein degradation in response to various stimuli. Several mechanisms are involved [23].One of the mechanisms responsible for protein degradation is the Ubiquitin-Proteasome System (UPS). The proteasome, a large protease, recognizes and degrades proteins tagged with ubiquitin molecules by E3 UB-protein ligase. Two of these ligase, MAFbx and MuRF1, are involved in muscle atrophy as they show increased activity in response to several stimuli [45].Another long-studied system involved in cell turnover is the Autophagy-Lysosome System, which is used in the degradation of cellular components in stressful situations of various kinds or in the event of nutritional deficiency through the formation of organelles called auto-phagolysosomes that are rich in lysosomal proteins. One of the tissues in which this system is most active is skeletal muscle: mitophagy—autophagy that selectively involves mitochondria—plays a role in muscle remodeling in atrophic muscle, in which the mitochondrial make-up is altered and damaged by denervation or fasting. Its uncontrolled and dysregulated action appears to be involved in the protein degradation observed during muscle atrophy [2,46].

3.1. Systemic Inflammation and Cytokine Dysregulation

Systemic inflammation is a central factor in the development of ICU-AW. Critical illness, particularly sepsis, triggers a widespread inflammatory response, characterized by the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines lead to muscle catabolism by stimulating the UPS, resulting in accelerated muscle protein degradation. Furthermore, these cytokines impair mitochondrial function, promoting oxidative stress and further contributing to muscle atrophy. It also appears that the activation of the TGF-β/MAPK pathway following stress stimuli, in association with the ubiquitine proteasome system (UPS) pathway, may play a role in muscle loss [2,47].

3.2. Oxidative Stress and Mitochondrial Dysfunction

Mitochondrial dysfunction plays a crucial role in ICU-AW. Critical illness leads to excessive production of reactive oxygen species (ROS) and a concomitant reduction in antioxidant defenses. The accumulation of ROS damages cellular components, including proteins, lipids, and mitochondrial DNA, exacerbating muscle wasting [48]. For instance, oxidative stress triggered by the muscle-specific expression of a mutant superoxide dismutase protein leads to muscle atrophy, primarily through the activation of autophagy [46]. Moreover, mitochondrial dysfunction impairs adenosine triphosphate (ATP) production, causing bioenergetic failure and hindering muscle contractility and repair processes [49].

3.3. Microvascular and Endothelial Dysfunction

Endothelial dysfunction, common in critical illness, reduces blood flow to the muscles, contributing to muscle ischemia and damage. Capillary leakage and microvascular thrombosis impair oxygen and nutrient delivery, exacerbating mitochondrial dysfunction and muscle degradation. Inflammatory mediators and oxidative stress disrupt endothelial nitric oxide production, further impairing vasodilation and microcirculation [23,50].

3.4. Immobilization and Muscle Disuse

Prolonged immobilization in ICU patients is another critical contributor to ICU-AW. Immobilization accelerates muscle atrophy by enhancing proteolysis and reducing muscle protein synthesis. Disuse leads to a rapid loss of type II (fast-twitch) muscle fibers, which

are particularly vulnerable to atrophy, further impairing muscle strength [35,51,52]. Muscle activity and nutrient availability stimulate another well-studied signaling pathway, the IGF1-Akt pathway. Akt, also known as protein kinase B, responds to several factors, including the growth factor IGF1. This kinase regulates both protein synthesis and protein degradation by acting on specific targets. Specifically, Akt promotes protein synthesis by activating mTOR and simultaneously inhibits protein degradation by suppressing the transcription factor FoxO. When FoxO is active, it promotes muscle degradation by enhancing the expression of muscle-specific ubiquitin ligases, such as Atrogin-1 and MuRF1, which are critical mediators of protein breakdown in muscle tissue [46].

3.5. Neuromuscular Involvement

In addition to direct muscle injury, ICU-AW can involve peripheral nerve dysfunction, leading to critical illness polyneuropathy (CIP). Nerve injury is driven by factors such as inflammation, oxidative stress, and metabolic disturbances. Axonal degeneration of motor and sensory fibers is commonly observed in CIP, contributing to the overall muscle weakness. Electrophysiological studies reveal reduced nerve conduction velocities and denervation potentials in affected patients [50,51]. A summary diagram of all the different pathogenetic mechanisms is shown in Figure 1.

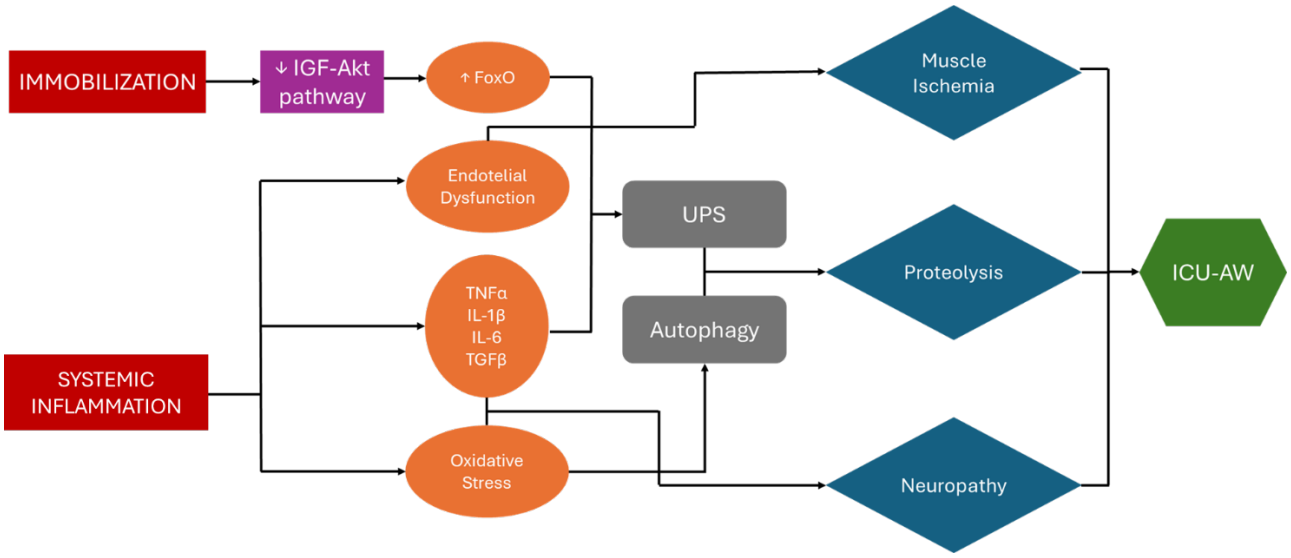


Figure 1. Pathogenesis of ICU-AW. Systemic inflammation associated with critical illness and prolonged immobilization are major contributors to ICU-acquired weakness (ICU-AW). Pro-inflammatory cytokines drive an increase in proteolysis via activation of the ubiquitin-proteasome system. Concurrently, oxidative stress from inflammatory processes leads to mitochondrial dysfunction and dysregulated activation of autophagy pathways. Systemic illness further induces endothelial dysfunction, promoting muscle ischemia. Extended immobilization disrupts the IGF-Akt signaling pathway, diminishing its activity and resulting in excessive FoxO activation, which amplifies the ubiquitin-proteasome system's effects. *Abbreviations*. UPS = Ubiquitin-Proteasome System; ICU-AW = Intensive Care Unit-Acquired Weakness.

4. Diagnosis

The diagnosis of ICU-AW is primarily clinical. The main criterion for diagnosing ICU-AW is the presence of symmetrical, progressive muscle weakness affecting all four limbs, while typically sparing the facial muscles. The diaphragm is often involved, which can complicate weaning from mechanical ventilation. Unlike other neuropathies, such as Guillain–Barré Syndrome, the onset of ICU-AW follows the critical illness, rather than preceding it [53–55].

4.1. Medical Research Council (MRC) Scale

The first step in the diagnosis of ICU-AW is to assess muscle strength in critically ill patients who are awake and cooperative. Manual muscle testing using the Medical Research Council (MRC) scale is the most widely accepted bedside tool. A sum score of less than 48 out of a possible 60 points across 12 muscle groups is indicative of ICU-AW. However, the ability to perform a reliable MRC test depends on patient consciousness, cooperation, and the absence of sedation [56].

4.2. Electrophysiological Studies

ICU-AW can have different pathogenic substrates, including critical illness polyneuropathy, critical illness myopathy, a combination of both, or muscle atrophy due to disuse. It is possible to refer to the set of neuromuscular diseases acquired in the ICU with the acronym CRYMINE (critical illness myopathy and/or neuropathy). To distinguish between CIP and CIM, electrophysiological studies are primarily used, such as nerve conduction studies (NCS) and electromyography are valuable adjuncts. By using NCS, it is possible to determine both compound motor action potentials (CMAPs) and sensory nerve action potentials (SNAPs). These measurements allow for the assessment of motor and sensory nerve function, respectively, and are critical in differentiating between neuropathic and myopathic causes of weakness in ICU patients. CMAPs reflect the overall response of the motor nerve and muscle, while SNAPs provide insights into the function of sensory nerves. Electromyography (EMG), on the other hand, assesses motor unit potential (MUP) amplitudes, durations, and fiber recruitment patterns. MUP amplitudes indicate the size and number of muscle fibers innervated by a single motor neuron, while MUP durations reflect the overall temporal profile of the motor unit's activity. The recruitment patterns assess the ability of the nervous system to activate additional motor units during muscle contraction, providing insights into neuromuscular integrity. CIP has reduced CMAP amplitudes and reduced SNAP amplitudes, while CIM has reduced CMAP amplitudes but normal SNAP amplitudes. Furthermore, on one hand they have spontaneous fibrillation potentials and sharp waves on EMG, but on the other hand CIP has high-amplitude polyphasic MUPs and CIM has low-amplitude MUPs with early recruitment. The peroneal nerve test (PENT) can be used as a simple and standardized electrophysiological method with good accuracy [54–58]. The main electrophysiological characteristics of CIP, CIM and CINM are described in Table 2.

Table 2. Electrophysiological diagnosis.

Condition	Definition	ENG	EMG
CIP References [56,58]	A polyneuropathy characterized by sensory and motor axonal damage, marked by reduced nerve responsiveness and loss of axons, while myelin remains intact.	Reduced CMAP and SNAP amplitudes and normal nerve conduction velocity.	Spontaneous fibrillation potentials, sharp waves and long duration, high-amplitude polyphasic MUP.
CIM References [56,58]	An acute primary myopathy characterized by reduced excitability of muscle membranes, loss of myosin filaments, muscle fiber atrophy, and tissue necrosis.	Reduced CMAP amplitudes, normal SNAP amplitudes and normal conduction velocities.	Spontaneous fibrillation potentials, sharp waves and short duration, low-amplitude MUP with early recruitment.
CINM References [56,58]	A combination of CIP and CIM.	Reduced CMAP and SNAP amplitudes and 8 normal conduction velocities.	A combination of CIP and CIM.

Abbreviations. CIP = critical illness polyneuropathy; CIM = critical illness myopathy; CINM = critical illness neuromyopathy; CMAP = compound motor action potential; SNAP = sensory nerve action potential; MUP = motor unit potential.

4.3. Neuromuscular Ultrasound (NMUS)

Since the previously described techniques are complex and not easily applied in routine practice, studies are focusing on NMUS as a tool to support the clinical diagnosis of ICU-AW. Although no reference standards have been established yet, ultrasounds allow for the assessment of both the muscle and nerve components. Specifically, ultrasounds can evaluate muscle mass reduction and increased muscle echogenicity, which, respectively, reflect changes in muscle quantity and quality. Target muscles in various studies include the biceps brachii, quadriceps femoris, and tibialis anterior. Similarly, the ultrasound assessment of nerve echogenicity in the transverse section, which will typically be reduced, as well as the nerve's cross-sectional area, can help estimate the presence of polyneuropathy, though it does not differentiate its type [59,60].

Additionally, especially in intensive care settings, ultrasound can estimate diaphragmatic function and predict the effectiveness of the patient's ventilatory response. This is primarily achieved by measuring diaphragmatic thickness at the end of expiration and inspiration, followed by calculating the diaphragmatic thickening fraction (TF) [61].

5. Management and Therapeutic Strategies

In our view, the proper management of ICU-AW and its clinical consequences requires a comprehensive, 360-degree approach to patient care. We emphasize the importance of a multidisciplinary team to effectively integrate the necessary preventive and therapeutic strategies. According to our opinion, the management of ICU-AW can be divided into three fundamental phases, which are not necessarily sequential but often occur simultaneously: prevention, early recognition, and effective treatment.

5.1. Prevention

Addressing the risk factors for the development of neuromyopathy is the first essential step in managing this clinical condition. A comprehensive assessment of patients, particularly geriatric patients, can effectively address risk factors for in-hospital death. Considering that frail in-patients are at an increased risk of death and complications, studies have demonstrated that functional assessments of surgical [62] and COVID-19 [63] patients can predict the risk of in-hospital death. It can be hypothesized that this approach could be effectively extended to critically ill patients, regardless of the cause.

Timely and effectively treating sepsis is crucial in minimizing the widespread negative effects it has on the body, including multi-organ dysfunction, and in preventing prolonged stays in the ICU, which expose patients to a cascade of risk factors leading to the development of ICU-AW. Additionally, reducing the impact of the cytokine storm that accompanies severe infection can mitigate its detrimental effects on neuromuscular function, based on what was previously said about the role of cytokines in protein degradation [47,64].

A key element in preventing ICU-AW is reducing the length of stay in the ICU. Shortening the duration of ICU admission not only decreases patient immobility, but also limits exposure to additional nosocomial infections, which could worsen the clinical condition. Prolonged immobility is a major contributor to the development of muscle atrophy and polyneuropathy. Promoting early mobilization is thus a fundamental strategy, not only for prevention but also therapeutically, as it helps preserve muscle strength and functionality [3]. To achieve this, reducing the time spent on mechanical ventilation is crucial. Prolonged mechanical ventilation can lead to diaphragmatic dysfunction, further complicating the clinical picture and hindering the patient's recovery. Reducing ventilation time not only improves diaphragm function but also facilitates faster recovery and lowers the risk of ICU-AW [25,65].

Among the risk factors considered, hyperglycemia is one of the most extensively studied and frequently observed in critically ill patients. The literature shows that maintaining optimal blood glucose levels through insulin therapy has a beneficial effect on both the central and peripheral nervous systems of ICU patients, helping to prevent the development of polyneuropathy and consequently reducing dependence on mechanical ventilation [31]. Moreover, a study conducted on mechanically ventilated patients highlights that early mobilization not only helps prevent disuse muscle atrophy, but also promotes euglycemia and reduces mechanisms of insulin resistance, presenting a valid alternative to insulin therapy [30]. Therefore, we believe that the metabolic status of the patient should be considered a priority in the management of critically ill patients.

In the management of ICU-AW, careful attention must be given to the drugs administered, as some medications may potentially contribute to the development of this condition. Although the scientific literature is not entirely consistent on this matter, with more recent studies tending to exonerate corticosteroids and neuromuscular blockers as primary risk factors [34,39], a prudent approach to pharmacological therapy remains essential. Overtreatment must be avoided, as prolonged and unmonitored use of certain drugs could still negatively impact muscle and neurological function.

In particular, corticosteroids have been linked in earlier studies to an increased risk of myopathy in critically ill patients [38], although more recent research has questioned this direct association. Similarly, prolonged use of neuromuscular blocking agents, which are sometimes necessary in the clinical management of mechanical ventilation, has been associated with possible muscle function impairment. However, recent evidence has shown conflicting results, highlighting that appropriate management of dose and treatment duration may mitigate these risks [27,34]. Thus, the therapeutic approach should always be individualized, avoiding both excessive and unjustified use of these medications, while prioritizing strategies that minimize the negative pharmacological impact on the patient.

5.2. *Early Recognition*

Prompt recognition of neuromuscular dysfunction in a critically ill patient is a crucial step in subsequent management, as it allows early intervention to halt the pathogenic mechanisms underlying this condition. There is no established gold standard for diagnosing ICU-AW, which often complicates effective identification [4]. As previously mentioned, validated methods include the MRC scale (Muscle power scale), which, however, requires active patient participation—a challenge in critical care settings. Electrophysiological studies such as EMG and NCS are also used but can be complex to perform.

Some studies have demonstrated the utility of the peroneal nerve test (PENT) as a screening method for identifying patients affected by ICU-AW. The literature indicates that a reduction in peroneal CMAP amplitude has a sensitivity of 100% and a specificity of 85.2% for identifying CIP or CIM when compared to standard electrophysiological studies [66]. Another study involving septic shock patients in intensive care confirmed the PENT's effectiveness in predicting such conditions and paired it with the measurement of sural sensory nerve action potentials (SNAP) to differentiate between CIM and CIP [56].

The use of PENT enables early and straightforward detection of ICU-AW, regardless of the patient's consciousness or ability to cooperate. These methods gain additional diagnostic value when combined with more recently applied techniques such as neuromuscular ultrasound, which are equally simple and quick to perform. In cooperative patients, the MRC scale remains a valid alternative.

5.3. Effective Treatment

In this article we analyze and summarize all the key points for the proper prevention and management of this clinical condition. We would like to emphasize that comprehensive patient management is crucial in this clinical process.

Patient mobilization and adequate nutrition are two cornerstones of the treatment of ICU-AW. One without the other is not sufficient; only a proper integration of both improves muscle function in patients [66]. Prolonged immobilization reduces muscle protein synthesis in response to the ingestion of exogenous proteins, likely due to the development of anabolic resistance to food intake, which appears to be one of the mechanisms underlying muscle atrophy from disuse [52].

One of the most effective interventions to prevent ICU-AW is early mobilization of patients. Initiating physical therapy and encouraging movement as soon as medically feasible can help maintain muscle strength and function. Patient mobilization not only helps prevent atrophy but also markedly improves patients' glycemic and metabolic compensation [30]. In the ICU, providing patients with physical therapy improves the strength of respiratory muscles, leading to an increase in ventilator-free days [67]. A 2014 study conducted on a population of septic patients who were ventilated for more than 48 h and admitted to the ICU for over 4 days suggests that adding functional electrical stimulation (FES)-cycling to traditional physical therapy methods appears to improve muscle performance upon awakening from sedation, while also reducing the incidence of delirium [68].

Nutritional support plays a vital role in preventing muscle wasting. Ensuring that patients receive adequate protein and caloric intake is crucial for maintaining muscle mass and supporting recovery [69]. Several studies examine the role of nutrition in these categories of patients, focusing particularly on the methods, timing, and composition of an adequate and effective nutritional approach. The literature is not fully consistent on the optimal nutritional approach regarding energy intake and protein requirements for critically ill patients. It appears that both complete starvation and overfeeding during the early phase of critical illness should be avoided as they can be harmful. A significant focus is on determining the appropriate protein intake. Current guidelines recommend a protein intake of 1.2–1.5 g/kg/day, which has been associated with reduced mortality. However, some studies suggest higher protein doses, exceeding 1.5 g/kg/day.

Nonetheless, caution is advised with high protein intake early in the illness, whether administered enterally or parenterally, as some studies have shown a direct association between increased protein intake and prolonged ICU stays, higher mortality, and even reduced muscle mass. This negative correlation between high protein or amino acid intake and poor patient outcomes may be explained by the suppression of the beneficial effects of autophagy, which helps clear damaged cells [69–71]. This effect is particularly evident in septic patients, where autophagy facilitates the clearance of intracellular bacterial products. A 2014 study highlighted that a high protein intake as early as the fourth day of ICU admission (defined as >1.2 g/kg) was associated with lower hospital mortality, but only in non-septic and non-overfed patients. In septic patients, the situation is more complex and further research is needed to provide specific recommendations [71]. In summary, in the absence of contraindications, it is appropriate to initiate EN within 24–48 h at a low dose, gradually increasing it to meet the rising metabolic demands for tissue repair [70]. In animal models, beta-hydroxybutyrate (3-HB), produced from fatty acid metabolism during ketogenesis, has shown a protective effect on muscle. Parenteral supplementation of 3-HB appears to offer muscle protection, suggesting its potential as a preventive strategy against muscle weakness in critically ill human patients [15]. Among emerging therapies, targeting the ubiquitin-proteasome system seems promising. Developing IGF-1 analogs selective for muscle Akt, which lack the cancer-promoting risks of IGF-1, could combat muscle loss,

though it must be noted that inhibiting protein degradation might lead to the accumulation of misfolded proteins [46].

The management of ICUAW requires a comprehensive, multidisciplinary approach. This involves coordination between intensivists, physiotherapists, nutritionists, and nursing staff to develop and implement individualized care plans for each patient.

6. Conclusions

In conclusion, the management of ICU-AW demands a multifaceted approach that includes early detection, prevention, and effective treatment strategies. ICU-AW arises from a combination of CIP, CIM and muscle atrophy due to disuse, all exacerbated by prolonged immobility and mechanical ventilation. Early diagnosis is pivotal, and employing a variety of tools, such as the MRC scale; electrophysiological studies and neuromuscular ultrasound (NMUS) offer reliable options for recognizing ICU-AW, particularly in unresponsive or non-cooperative patients.

Nutritional support plays a significant role in preserving muscle mass and function. Adequate protein intake and caloric support have been shown to prevent further muscle degradation, particularly when aligned with early mobilization. Implementing a tailored nutrition plan ensures that patients have the necessary nutrients to mitigate muscle waste. Moreover, early and progressive physiotherapy is crucial in both preventing and treating ICU-AW. Regular mobilization exercises, passive or active, reduce immobility-related complications, preserve muscle function, and improve overall outcomes. This combination of physical rehabilitation and nutrition helps counterbalance the muscle loss that occurs during extended ICU stays. Lastly, minimizing pharmacological risks, such as the overuse of corticosteroids and neuromuscular blocking agents, remains essential in preventing ICU-AW.

Altogether, a comprehensive and individualized approach involving early diagnosis, multidisciplinary care, nutrition, physiotherapy, and careful pharmacological management is key to improving outcomes for patients with ICU-AW.

7. Methods

The search was performed between September and November 2024 in the PubMed database. English-language original papers, short communications, clinical trials, randomized controlled trials, meta-analyses, letters, editorials, and articles were evaluated. Emphasis was placed on the selection of original papers and randomized controlled trials filtered for the last five years, whenever possible.

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