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Review

Intensive care unit-acquired weakness: Recent insights

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ABSTRACT

Intensive care unit-acquired weakness (ICU-AW) is a common complication in critically ill patients and is associated with a variety of adverse outcomes. These include the need for prolonged mechanical ventilation and ICU stay; higher ICU, in-hospital, and 1-year mortality; and increased in-hospital costs. ICU-AW is associated with multiple risk factors including age, underlying disease, severity of illness, organ failure, sepsis, immobilization, receipt of mechanical ventilation, and other factors related to critical care. The pathological mechanism of ICU-AW remains unclear and may be considerably varied. This review aimed to evaluate recent insights into ICU-AW from several aspects including risk factors, pathophysiology, diagnosis, and treatment strategies; this provides new perspectives for future research.

Introduction

Intensive care unit-acquired weakness (ICU-AW) refers to the clinical diagnosis of muscle weakness in critically ill patients, which cannot be attributed to causes other than critical illness.[1] ICU-AW is typically systemic and symmetrical; although it affects limb (proximal more than distal) and respiratory muscles; the facial and ocular muscles remain unaffected.[2,3] The clinical phenotype of ICU-AW may be heterogeneous owing to multiple factors including age, degree of comorbidity, length of ICU stay, and receipt of mechanical ventilation.[4] ICU-AW may originate from either a neurogenic disorder, namely, critical illness polyneuropathy (CIP), a myogenic disorder known as critical illness myopathy (CIM), or a combination of both (known as critical illness neuromyopathy).[5] The prevalence of ICU-AW varies considerably depending on the study population, risk factors, time of assessment, diagnostic methods, pre-hospital muscle function, and overall functional status.[6] A systematic review that included 31 studies reported a median prevalence of 43% (interquartile range: 25–75), with a higher incidence among patients with sepsis.[7]

ICU-AW is a common complication in critically ill patients and is associated with adverse outcomes including prolonged mechanical ventilation and ICU stay; increased hospitalization costs; and higher ICU, in-hospital, and 1-year mortality.[2,8] Cumulative evidence suggests that ICU-AW may also lead to adverse outcomes in the long term after discharge; these include the post-intensive care syndrome, which is characterized by persistent physical, mental, and cognitive dysfunction after ICU discharge. As this has a significant impact on long-term prognosis, including functional outcomes and survival,[9] survivors often experience permanent disability; this has considerable impact on their quality of life and is medical resource-intensive. As ICU-AW has gained increasing attention in recent years, this review evaluated recent insights into the condition from multiple aspects including risk factors, pathophysiology, diagnosis, and treatment strategies, with the aim of providing directions for future research.

Risk Factors

Independent risk factors associated with ICU-AW were identified and classified into modifiable or non-modifiable categories (Figure 1).

Modifiable risk factors

These risk factors include hyperglycemia, administration of parenteral nutrition, use of certain drugs for treating critically ill patients, and immobilization. In this context, a prospective ob-

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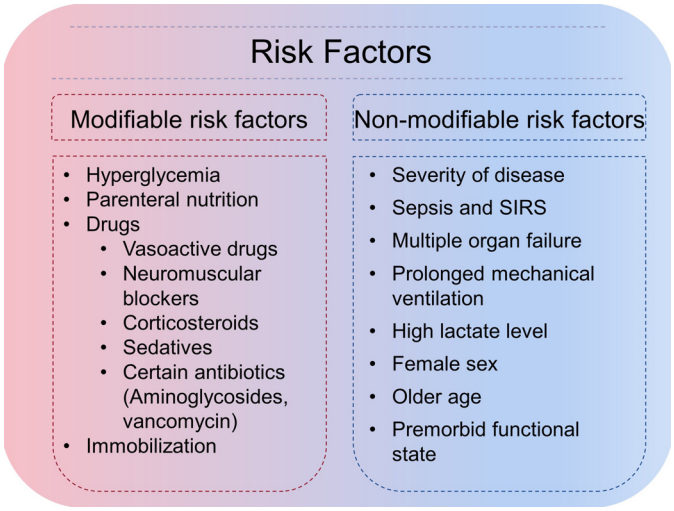

Figure 1. Risk factors for ICU-AW. The identified factors were classified as modifiable and non-modifiable.
ICU-AW: Intensive care unit-acquired weakness; SIRS: Systemic inflammatory response syndrome.

servational study demonstrated an obvious association between levels of hyperglycemia and critical illness polyneuromyopathy during ICU hospitalization.[10] Another retrospective study reported a link between hyperglycemia and paraplegia in adults with acute respiratory distress syndrome.[11] Randomized controlled trials have also found that strict blood glucose control decreases morbidity and mortality in critically ill patients and reduces the occurrence and development of critical illness-related polyneuropathy/myopathy.[12,13] Hyperglycemia has therefore been considered to be an independent risk factor for ICU-AW. Notably, reports have shown parenteral nutrition to be a risk factor for CIP.[14]

The administration of vasoactive drugs (mainly β-adrenergic receptor agonists) has also been found to increase the risk of developing ICU-AW; the dosage and course of treatment also influence the outcomes.[6] In this context, a meta-analysis showed a significant correlation between the use of corticosteroids and ICU-AW.[15]; in another meta-analysis on critically ill patients with sepsis, corticosteroids increased the risk of neuromuscular weakness.[16] However, a prospective and planned subgroup analysis of randomized controlled trials showed that corticosteroids, which are known to cause hyperglycemia and insulin resistance, may not adversely impact the development of CIP/CIM; they may even have protective effects in cases where normal blood glucose levels are maintained using insulin therapy.[13] In regard to drugs such as neuromuscular blockers, some prospective studies have shown that their use may contribute to the development of CIP/CIM.[13,14] However, other prospective studies, including observational studies and randomized controlled trials, have not confirmed the negative effect of neuromuscular blockers.[17,18] As sedative use often coexists with other risk factors, and these play a synergistic role, the relationship between sedatives and ICU-AW may be indirect.[19] Studies have found it difficult to distinguish between the effects of sedatives and those of sedation-induced immobility and bed rest.

In this context, a study found the duration of bed rest during critical illness to be the only factor consistently associated with muscle weakness over a 24-month period of follow-up (after ICU discharge); this indicates the potential importance of reducing bed rest duration for interventions during a critical illness.[17] Notably, certain antibiotics including aminoglycosides and vancomycin have also been reported to be independently associated with the development of ICU-AW.[20–22]

Non-modifiable risk factors

The severity of the disease is an important factor in critically ill patients. Previous studies have demonstrated higher severity of disease, sepsis and inflammation, multiple organ failure, and longer periods of mechanical ventilation and ICU stay to be predictive for the development of ICU-AW.[23] In this context, sepsis, systemic inflammatory response syndrome, and multiple organ failure were considered as key factors when CIP was first described.[5,20,24,25] Notably, associated sepsis was often present in early reports on cases of CIP.[24,26] Although mechanical ventilation is a risk factor, its relationship with ICU-AW may be mutual.

Evidence suggests that prolonged mechanical ventilation may increase the risk of developing the condition, which may in turn increase the risk of adverse outcomes including prolonged mechanical ventilation and weaning failure.[7,27] Notably, a meta-analysis found high lactate levels to be a risk factor for ICU-AW.[20]

Age and gender have also been identified as independent risk factors. In this regard, women were found to have a higher risk of weakness than men and the risk was greater in older patients than in their younger counterparts.[20,28] The premorbid functional state is also known to have a certain impact, and disability or frailty may influence the severity of weakness.[20] Premorbid obesity has not only been found to protect against lean tissue wasting, but it also prevents muscle weakness during critical illness;[29] it therefore acts as a protective factor against the development of ICU-AW and muscle atrophy.

Pathophysiology

The pathological mechanism of ICU-AW is complex and has not been completely clarified. Multiple mechanisms may be involved in regulating muscle weakness (Figure 2).

Protein imbalance

Continuous protein turnover in the muscles maintains the metabolic balance between protein synthesis and proteolysis. This balance is crucial in the muscle tissue and enables the organism to respond to rapid changes. An increase in age slows anabolism, creating a discrepancy between the average rates of protein anabolism and catabolism; this leads to a negative protein balance and gradually induces net loss of skeletal muscle, thereby promoting the occurrence of sarcopenia.[30] In critically ill patients, the balance between protein anabolism and catabolism may be disrupted by sepsis, the development of systemic inflammatory response syndrome, immobilization, and other causes. This is induced by the response of the body to certain stimuli or changes. These include activation of the sympathetic nervous system, release of catabolic hormones (e.g., catecholamines and glucocorticoids), and secretion of pro-inflammatory cytokines; these activate massive proteolysis and

resistance to anabolism and lead to muscle atrophy and weakness.[31]

Decreased protein synthesis

Insulin/insulin-like growth factor (IGF-1) signaling

The pathway involving insulin/IGF-1 and serine/threonine kinase (Akt) constitutes the main anabolic signaling cascade.[32] Akt activation increases protein synthesis via activation of the mTOR pathway. It also phosphorylates the downstream transcription factor, FOXO, preventing its translocation into the nucleus and rendering it inactive. It further inhibits the expression of E3 ubiquitin ligases (MuRF1 and atrogin-1), thereby inhibiting proteolysis.[33] In addition to activating the Akt signaling pathway, IGF-1 activates the mitogen-activated protein kinase cascade and promotes myoblast proliferation.[32]

Muscle levels of IGF-1 have been demonstrated to decline in the setting of sepsis; this is strongly associated with a reduction in the rate of muscle protein synthesis.[34] Conversely, the implantation of IGF-1-containing slow-release pellets in the muscles of septic mice has been found to increase muscle protein synthesis and potentially reduce proteolysis; this effectively improves the loss of muscle mass caused by sepsis, thereby slowing down the sepsis-induced muscle atrophy response.[35] IGF-1 is also reduced in the setting of muscle wasting; this may represent another mechanism of IGF-1 signaling inhibition in patients with ICU-AW.[32]

mTOR signaling

As the main regulator of anabolism, mTOR promotes anabolic processes and regulates biological processes (such as cell growth, proliferation, protein synthesis, and energy metabolism) following stimulation by growth factors, nutrients (amino acids), insulin, and other signals.[33] The signal transmitted to downstream eukaryotic translation initiation factor 4E-binding protein1 and S6 kinase (S6K1) after mTOR activation regulates protein translation.[36] In the non-phosphorylated state, 4EBP1 binds tightly to the messenger ribonucleic acid (mRNA) cap-binding subunit, eukaryotic translation initiation factor-4E (eIF4E) of the eIF4F complex; this inhibits eIF4E-mediated initiation of protein synthesis.[37] Phosphorylation of 4EBP1 by mTOR activation releases eIF4E; this facilitates the initiation of ribosomal cap-dependent translation.[33] As a downstream target of mTOR, S6K1 can activate the S6 protein in the 40S ribosomal subunit; this promotes the recruitment of 40S ribosomal subunits into the activated translation polymers after phosphorylation. It can also phosphorylate some substrates, such as eIF2K and eIF4B, during the process to promote translation.[38]

Studies have shown that sepsis leads to a decrease in mTOR activity and reduces the phosphorylation of 4E-BP1 and S6K1.[39] The inhibition of mTOR kinase activity may be partly attributed to the overproduction of pro-inflammatory cytokines; this is evident from the fact that specific inhibitors targeting these cytokines are able to prevent a reduction of 4E-BP1 and S6K1 phosphorylation induced by sepsis and restore muscle protein synthesis.[40]

Increased protein degradation

Metabolic stress represents a survival mechanism for the adaptive survival of the body during critical illnesses. However, it may lead to an imbalance in bodily function and cause degradation and loss of muscle protein in addition to other consequences. The protein degradation process involves mul-

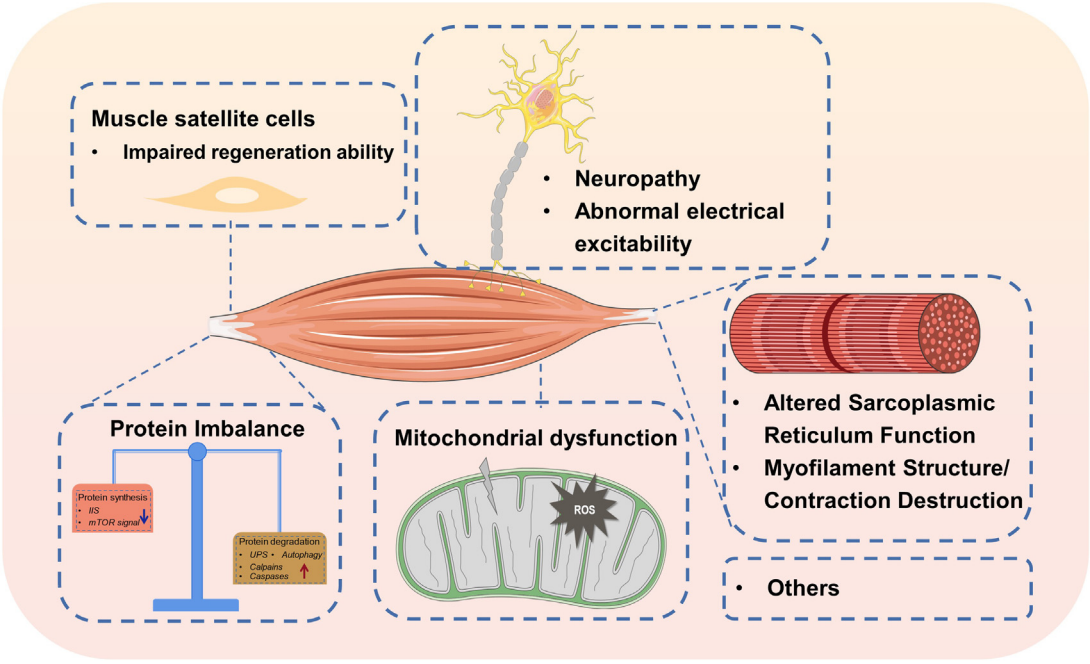

Figure 2. Mechanisms of ICU-AW. Multiple mechanisms involved in the regulation of ICU-AW include an imbalance between protein synthesis and degradation, dysfunction of mitochondria, alterations in the function of the sarcoplasmic reticulum, destruction of myofilament structure, neuropathy, abnormal electrical excitability, and other mechanisms such as impairment in muscle satellite cells. ICU-AW: Intensive care unit-acquired weakness; IIS: Insulin/IGF-1 signaling; UPS: Ubiquitin-proteasome system; ROS: Reactive oxygen species.

tiple pathways including the ubiquitin-proteasome, autophagy-lysosomal, calpain, and caspase pathways.[32]

Ubiquitin-proteasome system (UPS)

The UPS plays a major role in the proteolysis of muscle tissue; evidence suggests that it exhibits increased activity during the acute phase of muscle loss in animal models of critical illness (sepsis and burns) and in critically ill patients.[41] The key regulatory protein of this system is ubiquitin ligase, which binds to the target for degradation via precise protein-to-protein interactions; this ensures specificity for this proteolytic system.[42] The ubiquitin ligases, MuRF1 and atrogin-1, are key positive regulators of UPS-mediated muscle proteolysis and are considered to play a key role in muscle atrophy.[43–45] Studies have confirmed an increase in protein ubiquitination in the muscles of patients with ICU-AW; this is accompanied by damage to the structure of myosin filaments.[46] The levels of mRNA related to genes involved in the UPS are also increased in the muscles of patients with sepsis.[47] In addition, proteasome activity is enhanced in the respiratory and limb muscles of ICU patients with sepsis; this is indicative of increased muscle proteolysis.[48] In animal models, sepsis has been found to lead to respiratory and limb muscle atrophy; this is accompanied by elevated levels of mRNA for two key E3 ligases, namely, Fbox32 (atrogin-1) and Trim63 (MuRF).[49]

Autophagy-lysosomal system

The autophagy-lysosomal system also represents one of the major quality control systems in muscles. Autophagy, a necessary metabolic process for homeostasis maintenance, plays a crucial role in skeletal muscle homeostasis. It may be categorized into three different types, namely, chaperone-mediated autophagy, microautophagy, and macroautophagy.[50] The process is regulated by a variety of factors including hypoxia, infection, stress, and nutrient deficiencies, which may influence the expression and function of autophagy-related proteins. Autophagy plays an important role in the maintenance of muscle mass and integrity.[51] It is therefore essential that a relatively balanced state is maintained; this is because an increase in autophagy activity has been shown to lead to muscle atrophy and a decrease may contribute to the development of certain muscle diseases.[52,53] In this context, a study found that mechanical ventilation could lead to diaphragm disuse and activation of the autophagy-lysosome pathway; the process is characterized by autophagosome formation and an increase in the expression of autophagy-related genes.[54]

Calpains and caspases

Calpains are also associated with the development of ICU-AW. These are calcium-dependent cysteine proteases that are inactive under basic conditions,[55] and their activity is regulated by calcium and calpastatin.[56] There are at least 14 members of the calpain family; some are widely expressed in a variety of tissues (e.g., calpain-1 and calpain-2) and some are tissue-specific. Calpain-3, also known as p94, is specifically expressed by muscle tissue.[56] The expression and activity of calpain-1 and calpain-2 are increased in muscle atrophy,[57] while calpain-3 may be downregulated in denervation atrophy;[58] this is associated with certain muscular dystrophies.[57] Studies suggest that the calpain system is activated in sepsis-induced muscle atrophy; this leads to increased protein degradation. Calpain activation also downregulates Akt activity in skeletal muscle, leading to a decrease in protein synthesis.[56] In a sepsis model, increased calpain activity was found to reduce contractile function during muscle atrophy.[59] Calpain activation therefore promotes proteolysis and loss of muscle strength.

The role of caspases in apoptosis and cell death is well recognized. They are now also considered to be involved in sepsis-induced myopathy and are related to muscle atrophy.[32] Evidence from animal models of infection suggests that caspases are activated in the diaphragm; they cleave cytoskeletal proteins, leading to loss of muscle strength in the diaphragm.[60]

Mitochondrial Dysfunction

As the “power plant” of living organisms, the mitochondria are responsible for energy conversion, biosynthesis, and signal transduction.[33] Sufficient energy is an important condition for muscle contraction; as the core organelles of energy supply, mitochondria are crucial for the process of adenosine triphosphate (ATP) production and are therefore important energy sources for muscle function.[33] Mitochondria are also involved in calcium homeostasis, production of reactive oxygen species, mediation of intracellular communication, and regulation of apoptosis. However, mitochondrial damage is associated with ATP deficiency, overproduction of reactive oxygen species, and cytochrome c release. Disruption and dysfunction of mitochondrial ultrastructure may lead to organ failure. Notably, mitochondrial dysfunction is a key factor in the development of ICU-AW in critical illnesses, particularly sepsis.[33] A vicious cycle can occur within mitochondria, in which an increase in free radical production (caused by sepsis) aggravates dysfunction, thereby leading to further free radical production.[32] Reports suggest that the expression and activity of mitochondrial respiratory chain complexes I, III, and IV are reduced in the muscles of critically ill patients; this may partly explain the phenomenon of muscle fatigue observed in ICU patients.[61] In this context, mitophagy is an important process of quality control that cleaves damaged organelles. Inhibition of this clearance may lead to progression of multiple organ dysfunction, thereby increasing the risk of death.[62] However, the accumulation of damaged mitochondria has been shown to cause degeneration of motor neurons and muscle fibers; this leads to ICU-AW or sarcopenia as muscle dysfunction progresses.[33]

Alterations in Sarcoplasmic Reticulum Function

Appropriate levels and changes in calcium levels are crucial for the contraction of muscle cells. This is mediated by the direct effect of calcium on myosin ATPase activity during the contraction cycle and by regulation of glycolysis and oxidative energy metabolism.[32] However, calcium also acts as an important regulator of protein breakdown by activating calpain and ubiquitination.[33] The sarcoplasmic reticulum is responsible for calcium binding and release in skeletal muscle; this contributes to calcium homeostasis. Sepsis has a significant negative effect on calcium homeostasis; it reduces the release of calcium in the sarcoplasmic reticulum, increases the sensi-

tivity of contractile proteins to calcium, affects membrane excitability in skeletal muscle, and leads to a decrease in muscle strength.[63]

Abnormal Electrical Excitability

Under physiological conditions, the permeability of cell membranes to Na^+, K^+, and possibly Ca^{2+} ions changes to accommodate normal electrophysiological stimulation; excitation is a necessary condition for action potential generation.[33] The resting potential energy increases after excitation and reaches the threshold potential for Na^+ channel opening. On entry of Na^+ into the cell, the inner aspect of the membrane becomes positively charged compared to the outer aspect; this results in depolarization. The K^+ channel subsequently opens to increase permeability to K^+, which flows out; the decrease in intracellular membrane potential causes repolarization.[33] Changes to membrane Na^+ pumps in sepsis can lead to disturbances in electrical excitability. Notably, inflammatory cytokines are neurotoxic and lead to chronic membrane depolarization, which is characterized by "denervation".[33] Inactivation of Na^+ channels in patients with ICU-AW may result in rapid and reversible hypoexcitability or non-excitability of nerves and muscle membranes, affecting nerve and muscle function.[41]

Neuropathy

Axonal degeneration represents one of the pathological changes in patients with CIP;[64] however, its pathogenesis remains unclear. Sepsis may cause microvascular changes in the endoneurium, increase vascular permeability, and allow penetration of toxic factors into nerve endings. In addition, intraneural edema caused by increased permeability may impair energy transmission in axons, leading to axonal death;[65] the direct toxic effects of hyperglycemia and mitochondrial dysfunction may contribute to this process.[5] In this context, evidence suggests that aggressive glycemic control reduces the risk of polyneuropathy (and myopathy) and the need for long-term mechanical ventilation.[12,13]

Others

The destruction of myofilament structure (as caused by tumor necrosis factor-α) or the disruption of mechanisms regulating the contraction process are potential factors that reduce muscle strength.[32] Impairment in the regeneration ability of muscle satellite cells is also one of the potential mechanisms of muscle atrophy. Muscle injury stimulates myoblasts (as muscle progenitor cells) to proliferate and promote cell repair and regeneration. The process involves the fusion of multiple myoblasts to form myotubes, which then integrate with the injured muscle.[66] However, the proliferation and differentiation of muscle satellite cells are inhibited in sepsis; this disrupts the regeneration and repair of injured muscles.[67,68] Notably, a recent study has demonstrated the role of cellular senescence in sepsis-induced muscle weakness; this may also be one of the mechanisms underlying the development of ICU-AW.[69]

A study on septic mice suggested that mitochondrial function is impaired in satellite cells during sepsis; transplantation of mesenchymal stem cells could improve skeletal muscle function.[67] Likewise, the regenerative ability of muscle satellite cells was found to be impaired in ICU survivors, with a reduction in the number of satellite cells after 6 months of ICU stay; this was indicative of a defect in the muscle repair process.[70]

Diagnosis of ICU-AW

ICU-AW is a clinical diagnosis that is obtained by evaluating muscle strength in the six major muscle groups using the Medical Research Council Score (MRC-SS) in an appropriate clinical environment. Patients with a total score of <48 and <36 are diagnosed with ICU-AW and severe ICU-AW, respectively.[6] The MRC-SS rates the strength of 12 predefined peripheral muscle groups (bilateral shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and foot dorsiflexors).[71] The hand-held dynamometer is considered to be an effective and reliable tool for screening ICU-AW; the threshold values for grip strength in ICU-AW are <11 kg for men and <7 kg for women.[72] As the dynamometer (similar to MRC-SS) requires patients to be awake and cooperative, the above diagnostic methods are difficult to implement in the setting of delirium, coma, and sedation.

Imaging techniques are also often used as evaluation tools and usually do not require patient cooperation. As a non-invasive examination tool, muscle ultrasound is an indispensable diagnostic tool in the ICU and can provide a repeatable and rapid assessment of muscle mass and structural changes at the bedside. However, muscle ultrasound has certain limitations, as it is difficult to determine whether a patient has ICU-AW when awake.[3] Neuromuscular ultrasound data can be quantified using computer software to calculate the average gray level of muscles and cross-sectional area and echo intensity of nerves.[73] It has been demonstrated to be a repeatable process for routine clinical diagnosis of patients with chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and chronic idiopathic axonal polyneuropathy.[3] Computed tomography also quantifies the size and mass of muscles, but is rarely used in clinical practice.[71]

Electrophysiological evaluation using electromyography and nerve conduction measurements can also be used to diagnose ICU-AW in unconscious/uncooperative patients.[5] Single nerve conduction studies are expected to replace time-consuming complete electrophysiological studies.[74] Direct muscle stimulation shows normal muscle excitability in uncooperative patients with CIP and decreased muscle excitability in patients with CIM.[6] These electrophysiological tests usually require professional equipment and well-trained technicians, and are cumbersome and time-consuming. Although muscle biopsy can provide important information that aids in the diagnosis of CIP/CIM, it is mostly used for scientific research owing to its invasiveness and the risks associated with clinical use.[6]

Treatment of ICU-AW

As there is currently no effective treatment for ICU-AW, its management mainly depends on prevention. It is therefore important to avoid or treat sepsis and inflammation early to reduce the risk of ICU-AW. Early treatment of sepsis can prevent the development of muscle damage mediated directly and indirectly by inflammation and promote early recovery of physical

function, thereby reducing the incidence of muscle weakness.[75] Although tight glycemic control prevents the development of ICU-AW,[13] there may be potential risks; studies have shown an increased risk of death with intensive glucose control, possibly due to hypoglycemia.[76] The optimal glucose levels remain controversial; however, findings from multicenter randomized controlled studies suggest that intermediate levels of blood glucose may be safer.[77] As parenteral nutrition is a risk factor for ICU-AW, early enteral nutrition should be advocated in critically ill patients.[78] In this context, early parenteral nutrition is associated with a higher risk of ICU-AW, impaired recovery, and prolongation of the duration of mechanical ventilation and ICU stay.[6,79]

In view of the potential negative effects of sedative drugs on the development of ICU-AW.[80], and the increased risk of ICU-AW in patients with immobilization,[6] a reduction in sedation and early initiation of activity are important strategies for its prevention and treatment. Mobilization represents an important component of the recovery process. Evidence suggests that early rehabilitation in critically ill patients is safe, improves outcomes, and improves muscle strength.[81] Early mobilization has been shown to have dual effects; it reduces the occurrence of ICU-AW and promotes the regulation of blood glucose to ensure compliance with the target range.[82] In this context, a single-center, parallel, randomized controlled trial found early mobilization to be the first known intervention that improved long-term cognitive impairment in ICU survivors after mechanical ventilation; it also played a beneficial role in other aspects including neuromuscular weakness and health-related quality of life.[83] In another international multi-center randomized controlled trial that was conducted in the surgical ICU setting, early goal-directed mobilization therapy increased the mobility level in patients, shortened the length of stay in the ICU and hospital, and improved functional independence at discharge.[84] A systematic review that included 14 studies with a total of 1753 patients found that active mobilization and rehabilitation in the ICU may improve mobility status and muscle strength; however, it had no impact on short- and long-term mortality.[85] Notably, a recent randomized controlled trial that included adult patients undergoing mechanical ventilation found a higher incidence of adverse events in the early mobilization group than in the usual care group.[86] In view of the limited evidence, further well-designed large-scale multi-center randomized controlled trials will be needed to evaluate the effects of active mobilization and rehabilitation.

Neuromuscular electrical stimulation (NMES) may be used as alternative therapy, especially in patients who cannot actively participate in physical therapy.[87] Interestingly, a randomized controlled trial that aimed to evaluate the effects of adding NMES to early mobilization showed better outcomes with the addition of NMES. The patients demonstrated a lower incidence of ICU-AW, better muscle strength, and shorter length of hospital stay.[88] Although some studies suggest that this therapy offers promise,[89] recent systematic reviews and meta-analyses have not shown any significant positive impact of NMES in terms of muscle strength, dependence on mechanical ventilation, and ICU stay.[90] The effects of NMES therapy therefore warrant further investigation.

Conclusions

ICU-AW is a frequent complication of critical illnesses, leading to various adverse consequences. It may be essential for persistent physical functional limitations among ICU survivors. Given its detrimental impact, future research must prioritize the prevention of this condition. In particular, the pathological mechanisms underlying the development of AW in the ICU and effective interventions warrant further investigation.

Author Contributions

Juan Chen: Writing – original draft, Conceptualization. **Man Huang:** Conceptualization, Writing – review & editing.

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Ethics Statement

Not applicable.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

[1] Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med 2009;37(10 Suppl):S299–308. doi:10.1097/CCM.0b013e3181b6ef67.
[2] Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med 2017;43(9):1270–81. doi:10.1007/s00134-017-4757-5.
[3] Piva S, Fagoni N, Latronico N. Intensive care unit-acquired weakness: unanswered questions and targets for future research. F1000Res 2019;8 F1000FacultyRev–508. doi:10.12688/f1000research.17376.1.
[4] Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med 2013;187(3):238–46. doi:10.1164/rccm.201205-0954SO.
[5] Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care 2015;19(1):274. doi:10.1186/s13054-015-0993-7.
[6] Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med 2020;46(4):637–53. doi:10.1007/s00134-020-05944-4.
[7] Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med 2014;190(12):1437–46. doi:10.1164/rccm.201411-2011ST.
[8] Kelmenson DA, Held N, Allen RR, Quan D, Burnham EL, Clark BJ, et al. Outcomes of ICU patients with a discharge diagnosis of critical illness polyneuromyopathy: a propensity-matched analysis. Crit Care Med 2017;45(12):2055–60. doi:10.1097/ccm.0000000000002763.

[9] Voiriot G, Oualha M, Pierre A, Salmon-Gandonnière C, Gaudet A, Jouan Y, et al. Chronic critical illness and post-intensive care syndrome: from pathophysiology to clinical challenges. Ann Intensive Care 2022;12(1):58. doi:10.1186/s13613-022-01038-0.
[10] Nanas S, Kritikos K, Angelopoulos E, Siafaka A, Tsikriki S, Poriazi M, et al. Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. Acta Neurol Scand 2008;118(3):175–81. doi:10.1111/j.1600-0404.2008.00996.x.
[11] Bercker S, Weber-Carstens S, Deja M, Grimm C, Wolf S, Behse F, et al. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med 2005;33(4):711–15. doi:10.1097/01.ccm.0000157969.46388.a2.
[12] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345(19):1359–67. doi:10.1056/NEJMoa011300.
[13] Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med 2007;175(5):480–9. doi:10.1164/rccm.200605-665OC.
[14] Garnacho-Montero J, Madrazo-Osuna J, García-Garmendia JL, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodóvar A, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med 2001;27(8):1288–96. doi:10.1007/s001340101009.
[15] Yang T, Li Z, Jiang L, Xi X. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. Crit Care 2018;22(1):187. doi:10.1186/s13054-018-2111-0.
[16] Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. Crit Care Med 2018;46(9):1411–20. doi:10.1097/CCM.0000000000003262.
[17] Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med 2014;42(4):849–59. doi:10.1097/ccm.0000000000000040.
[18] Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–16. doi:10.1056/NEJMoa1005372.
[19] Foster J. Complications of sedation in critical illness: an update. Crit Care Nurs Clin North Am 2016;28(2):227–39. doi:10.1016/j.cnc.2016.02.003.
[20] Yang T, Li Z, Jiang L, Wang Y, Xi X. Risk factors for intensive care unit-acquired weakness: a systematic review and meta-analysis. Acta Neurol Scand 2018;138(2):104–14. doi:10.1111/ane.12964.
[21] Wieske L, van Hest RM, Witteveen E, Verhamme C, Schultz MJ, van Schaik IN, et al. Is gentamicin affecting the neuromuscular system of critically ill patients? Intensive Care Med 2015;41(4):727–8. doi:10.1007/s00134-015-3731-3.
[22] Yang T, Li ZQ, Li HL, Zhou JX, Chen GQ. Aminoglycoside use and intensive care unit-acquired weakness: a systematic review and meta-analysis. PLoS ONE 2020;15(3):e0230181. doi:10.1371/journal.pone.0230181.
[23] De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288(22):2859–67. doi:10.1001/jama.288.22.2859.
[24] Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry 1984;47(11):1223–31. doi:10.1136/jnnp.47.11.1223.
[25] Bednarík J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuromyopathy. J Neurol 2005;252(3):343–51. doi:10.1007/s00415-005-0654-x.
[26] Zochodne DW, Bolton CF, Wells GA, Gilbert JJ, Hahn AF, Brown JD, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. Brain 1987;110(Pt 4):819–41. doi:10.1093/brain/110.4.819.
[27] Dres M, Jung B, Molinari N, Manna F, Dubé BP, Chanques G, et al. Respective contribution of intensive care unit-acquired limb muscle and severe diaphragm weakness on weaning outcome and mortality: a post hoc analysis of two cohorts. Crit Care 2019;23(1):370. doi:10.1186/s13054-019-2650-z.
[28] Chlan LL, Tracy MF, Guttormson J, Savik K. Peripheral muscle strength and correlates of muscle weakness in patients receiving mechanical ventilation. Am J Crit Care 2015;24(6):e91–8. doi:10.4037/ajcc2015277.
[29] Goossens C, Marques MB, Derde S, Vander Perre S, Dufour T, Thiessen SE, et al. Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness. J Cachexia Sarcopenia Muscle 2017;8(1):89–101. doi:10.1002/jcsm.12131.
[30] Dillon EL. Nutritionally essential amino acids and metabolic signaling in aging. Amino Acids 2013;45(3):431–41. doi:10.1007/s00726-012-1438-0.
[31] Preiser JC, Ichai C, Orban JC, Groeneveld AB. Metabolic response to the stress of critical illness. Br J Anaesth 2014;113(6):945–54. doi:10.1093/bja/aeu187.
[32] Bloch S, Polkey MI, Griffiths M, Kemp P. Molecular mechanisms of intensive care unit-acquired weakness. Eur Respir J 2012;39(4):1000–11. doi:10.1183/09031936.00090011.
[33] Kanova M, Kohout P. Molecular mechanisms underlying intensive care unit-acquired weakness and sarcopenia. Int J Mol Sci 2022;23(15):8396. doi:10.3390/ijms23158396.
[34] Lang CH, Frost RA. Role of growth hormone, insulin-like growth factor-I, and insulin-like growth factor binding proteins in the catabolic response to injury and infection. Curr Opin Clin Nutr Metab Care 2002;5(3):271–9. doi:10.1097/00075197-200205000-00006.
[35] Nystrom G, Pruznak A, Huber D, Frost RA, Lang CH. Local insulin-like growth factor I prevents sepsis-induced muscle atrophy. Metabolism 2009;58(6):787–97. doi:10.1016/j.metabol.2009.01.015.
[36] Ma XM, Blenis J. Molecular mechanisms of mTOR-mediated translational control. Nat Rev Mol Cell Biol 2009;10(5):307–18. doi:10.1038/nrm2672.
[37] Kincheloe GN, Roberson PA, Toro AL, Stanley BA, Stanley AE, Jefferson LS, et al. Loss of 4E-BPs prevents the hindlimb immobilization-induced decrease in protein synthesis in skeletal muscle. J Appl Physiol (1985) 2023;134(1):72–83. doi:10.1152/japplphysiol.00563.2022.
[38] Showkat M, Beigh MA, Andrabi KI. mTOR signaling in protein translation regulation: implications in cancer genesis and therapeutic interventions. Mol Biol Int 2014;2014:686984. doi:10.1155/2014/686984.
[39] Lang CH, Frost RA, Vary TC. Regulation of muscle protein synthesis during sepsis and inflammation. Am J Physiol Endocrinol Metab 2007;293(2):E453–9. doi:10.1152/ajpendo.00204.2007.
[40] Frost RA, Lang CH. mTor signaling in skeletal muscle during sepsis and inflammation: where does it all go wrong? Physiology (Bethesda) 2011;26(2):83–96. doi:10.1152/physiol.00044.2010.
[41] Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev 2015;95(3):1025–109. doi:10.1152/physrev.00028.2014.
[42] Batt J, Herridge M, Dos Santos C. Mechanism of ICU-acquired weakness: skeletal muscle loss in critical illness. Intensive Care Med 2017;43(12):1844–6. doi:10.1007/s00134-017-4758-4.
[43] Bodine SC, Latres E, Baumhueter S, Lai VK, Nunez L, Clarke BA, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 2001;294(5547):1704–8. doi:10.1126/science.1065874.
[44] Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, et al. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med 2014;40(4):528–38. doi:10.1007/s00134-014-3224-9.
[45] Gomes MD, Lecker SH, Jagoe RT, Navon A, Goldberg AL. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proc Natl Acad Sci U S A 2001;98(25):14440–5. doi:10.1073/pnas.251541198.
[46] Helliwell TR, Wilkinson A, Griffiths RD, McClelland P, Palmer TE, Bone JM. Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. Neuropathol Appl Neurobiol 1998;24(6):507–17. doi:10.1046/j.1365-2990.1998.00144.x.
[47] Tiao G, Hobler S, Wang JJ, Meyer TA, Luchette FA, Fischer JE, et al. Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. J Clin Invest 1997;99(2):163–8. doi:10.1172/jci119143.
[48] Klaude M, Fredriksson K, Tjäder I, Hammarqvist F, Ahlman B, Rooyackers O, et al. Proteasome proteolytic activity in skeletal muscle is increased in patients with sepsis. Clin Sci (Lond) 2007;112(9):499–506. doi:10.1042/cs20060265.
[49] Stana F, Vujovic M, Mayaki D, Leduc-Gaudet JP, Leblanc P, Huck L, et al. Differential regulation of the autophagy and proteasome pathways in skeletal muscles in sepsis. Crit Care Med 2017;45(9):e971–9. doi:10.1097/ccm.0000000000002520.
[50] Fleming A, Bourdenx M, Fujimaki M, Karabiyik C, Krause GJ, Lopez A, et al. The different autophagy degradation pathways and neurodegeneration. Neuron 2022;110(6):935–66. doi:10.1016/j.neuron.2022.01.017.
[51] Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, et al. Autophagy is required to maintain muscle mass. Cell Metab 2009;10(6):507–15. doi:10.1016/j.cmet.2009.10.008.
[52] Franco-Romero A, Sandri M. Role of autophagy in muscle disease. Mol Aspects Med 2021;82:101041. doi:10.1016/j.mam.2021.101041.
[53] Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell 2008;132(1):27–42. doi:10.1016/j.cell.2007.12.018.
[54] Hussain SN, Mofarrahi M, Sigala I, Kim HC, Vassilakopoulos T, Maltais F, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. Am J Respir Crit Care Med 2010;182(11):1377–86. doi:10.1164/rccm.201002-0234OC.
[55] Shapovalov I, Harper D, Greer PA. Calpain as a therapeutic target in cancer. Expert Opin Ther Targets 2022;26(3):217–31. doi:10.1080/14728222.2022.2047178.
[56] Smith IJ, Lecker SH, Hasselgren PO. Calpain activity and muscle wasting in sepsis. Am J Physiol Endocrinol Metab 2008;295(4):E762–71. doi:10.1152/ajpendo.90226.2008.
[57] Bartoli M, Richard I. Calpains in muscle wasting. Int J Biochem Cell Biol 2005;37(10):2115–33. doi:10.1016/j.biocel.2004.12.012.
[58] Stockholm D, Herasse M, Marchand S, Praud C, Roudaut C, Richard I, et al. Calpain 3 mRNA expression in mice after denervation and during muscle regeneration. Am J Physiol Cell Physiol 2001;280(6):C1561–9. doi:10.1152/ajpcell.2001.280.6.C1561.
[59] Supinski GS, Callahan LA. Calpain activation contributes to endotoxin-induced diaphragmatic dysfunction. Am J Respir Cell Mol Biol 2010;42(1):80–7. doi:10.1165/rcmb.2008-0275OC.
[60] Supinski GS, Callahan LA. Caspase activation contributes to endotoxin-induced diaphragm weakness. J Appl Physiol (1985) 2006;100(6):1770–7. doi:10.1152/japplphysiol.01288.2005.
[61] Preau S, Vodovar D, Jung B, Lancel S, Zafrani L, Flatres A, et al. Energetic dysfunction in sepsis: a narrative review. Ann Intensive Care 2021;11(1):104. doi:10.1186/s13613-021-00893-7.
[62] Wu Y, Yao YM, Lu ZQ. Mitochondrial quality control mechanisms as potential therapeutic targets in sepsis-induced multiple organ failure. J Mol Med (Berl) 2019;97(4):451–62. doi:10.1007/s00109-019-01756-2.
[63] Zink W, Kaess M, Hofer S, Plachky J, Zausig YA, Sinner B, et al. Alterations in intracellular Ca2+-homeostasis of skeletal muscle fibers during sepsis. Crit Care Med 2008;36(5):1559–63. doi:10.1097/CCM.0b013e318170aa97.
[64] Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014;370(17):1626–35. doi:10.1056/NEJMra1209390.
[65] Bolton CF. Neuromuscular manifestations of critical illness. Muscle Nerve 2005;32(2):140–63. doi:10.1002/mus.20304.

[66] Rochlin K, Yu S, Roy S, Baylies MK. Myoblast fusion: when it takes more to make one. Dev Biol 2010;341(1):66–83. doi:10.1016/j.ydbio.2009.10.024.
[67] Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun 2015;6:10145. doi:10.1038/ncomms10145.
[68] Mankowski RT, Laitano O, Darden D, Kelly L, Munley J, Loftus TJ, et al. Sepsis-induced myopathy and gut microbiome dysbiosis: mechanistic links and therapeutic targets. Shock 2022;57(1):15–23. doi:10.1097/shk.0000000000001843.
[69] Chen J, Chen XY, Cong XX, Wang S, Xu SB, Sun YT, et al. Cellular senescence implicated in sepsis-induced muscle weakness and ameliorated with metformin. Shock 2023;59(4):646–56. doi:10.1097/SHK.0000000000002086.
[70] C Dos Santos, Hussain SN, Mathur S, Picard M, Herridge M, Correa J, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med 2016;194(7):821–30. doi:10.1164/rccm.201512-2344OC.
[71] Teixeira JP, Mayer KP, Griffin BR, George N, Jenkins N, Pal CA, et al. Intensive care unit-acquired weakness in patients with acute kidney injury: a contemporary review. Am J Kidney Dis 2023;81(3):336–51. doi:10.1053/j.ajkd.2022.08.028.
[72] Parry SM, Berney S, Granger CL, Dunlop DL, Murphy L, El-Ansary D, et al. A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care 2015;19(1):52. doi:10.1186/s13054-015-0780-5.
[73] Witteveen E, Sommers J, Wieske L, Doorduin J, van Alfen N, Schultz MJ, et al. Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. Ann Intensive Care 2017;7(1):40. doi:10.1186/s13613-017-0263-8.
[74] Kelmenson DA, Quan D, Moss M. What is the diagnostic accuracy of single nerve conduction studies and muscle ultrasound to identify critical illness polyneuromyopathy: a prospective cohort study. Crit Care 2018;22(1):342. doi:10.1186/s13054-018-2281-9.
[75] Farhan H, Moreno-Duarte I, Latronico N, Zafonte R, Eikermann M. Acquired muscle weakness in the surgical intensive care unit: nosology, epidemiology, diagnosis, and prevention. Anesthesiology 2016;124(1):207–34. doi:10.1097/aln.0000000000000874.
[76] Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al., NICE-SUGAR Study Investigators Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367(12):1108–18. doi:10.1056/NEJMoa1204942.
[77] Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al., NICE-SUGAR Study Investigators Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97. doi:10.1056/NEJMoa0810625.
[78] Tortuyaux R, Davion JB, Jourdain M. Intensive care unit-acquired weakness: questions the clinician should ask. Rev Neurol (Paris) 2022;178(1–2):84–92. doi:10.1016/j.neurol.2021.12.007.
[79] Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374(12):1111–22. doi:10.1056/NEJMoa1514762.
[80] Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extrem Physiol Med 2015;4:16. doi:10.1186/s13728-015-0036-7.
[81] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874–82. doi:10.1016/s0140-6736(09)60658-9.
[82] Patel BK, Pohlman AS, Hall JB, Kress JP. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. Chest 2014;146(3):583–9. doi:10.1378/chest.13-2046.
[83] Patel BK, Wolfe KS, Patel SB, Dugan KC, Esbrook CL, Pawlik AJ, et al. Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial. Lancet Respir Med 2023;11(6):563–72. doi:10.1016/s2213-2600(22)00489-1.
[84] Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 2016;388(10052):1377–88. doi:10.1016/s0140-6736(16)31637-3.
[85] Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med 2017;43(2):171–83. doi:10.1007/s00134-016-4612-0.
[86] Hodgson CL, Bailey M, Bellomo R, Brickell K, Broadley T, et al., TEAM Study Investigators and the ANZICS Clinical Trials Group Early active mobilization during mechanical ventilation in the ICU. N Engl J Med 2022;387(19):1747–58. doi:10.1056/NEJMoa2209083.
[87] Files DC, Sanchez MA, Morris PE. A conceptual framework: the early and late phases of skeletal muscle dysfunction in the acute respiratory distress syndrome. Crit Care 2015;19(1):266. doi:10.1186/s13054-015-0979-5.
[88] Campos DR, Bueno TBC, Anjos JSGG, Zoppi D, Dantas BG, Gosselink R, et al. Early neuromuscular electrical stimulation in addition to early mobilization improves functional status and decreases hospitalization days of critically ill patients. Crit Care Med 2022;50(7):1116–26. doi:10.1097/CCM.0000000000005557.
[89] Burke D, Gorman E, Stokes D, Lennon O. An evaluation of neuromuscular electrical stimulation in critical care using the ICF framework: a systematic review and meta-analysis. Clin Respir J 2016;10(4):407–20. doi:10.1111/crj.12234.
[90] Zayed Y, Kheiri B, Barbarawi M, Chahine A, Rashdan L, Chintalapati S, et al. Effects of neuromuscular electrical stimulation in critically ill patients: a systematic review and meta-analysis of randomised controlled trials. Aust Crit Care 2020;33(2):203–10. doi:10.1016/j.aucc.2019.04.003.