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Advances in the Diagnosis and Treatment of ICU-Acquired Weakness

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Abstract: ***Intensive Care Unit-acquired weakness (ICU-AW) refers to generalized muscle weakness in ICU patients due to acute illness or its treatment, which cannot be explained by other causes. Given the variability in baseline conditions among ICU patients, the risk factors, diagnosis, and treatment of ICU-AW warrant further investigation. This article reviews the latest advancements in the diagnosis and management of ICU-AW, analyzing existing risk factors, clinical manifestations, diagnostic methods, and treatment and prevention strategies, with the aim of improving the clinical outcomes of ICU patients.***

Keywords: ICU-acquired Weakness, Risk factors, Clinical presentation, Diagnosis and treatment**.**

1. Introduction

ICU-acquired weakness (ICU-AW) refers to generalized muscle weakness in ICU inpatients due to acute illness or its treatment and other unexplained causes. In critically ill patients, the incidence of muscle weakness caused by primary neuromuscular dysfunction is less than 0.5% [1], with the vast majority of muscle weakness being secondary to the critical illness itself. ICU-AW can be divided into three subtypes: critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and critical illness polyneuromyopathy (CINM). The concept of ICU-AW was first proposed by Bolton et al. in 1983 [2], and in 2014, the American Thoracic Society drafted the ICU-AW guidelines, defining it as a clinical syndrome characterized by new-onset, symmetric muscle weakness of the limbs occurring during critical illness, not caused by the critical illness itself [3]. Due to the variability and severity of the underlying diseases in ICU patients, the diagnosis and treatment of ICU-AW are worthy of further study. This article aims to review the latest advances in the diagnosis and treatment of ICU-AW, with the hope of improving the clinical outcomes of ICU patients.

2. Epidemiology

The incidence of ICU-AW varies significantly across global studies, largely depending on the study population and the time of assessment. Among 31 studies, the median prevalence of ICU-AW was 43% [4]. One study indicated that the early incidence rate of ICU-AW was 31.7%, the late incidence rate was 50%, and the overall incidence rate was estimated to be 65.9% [5]. In surgical ICUs, 56-74% of patients exhibit symptoms of ICU-AW [6]. ICU-AW is a significant prognostic factor for ICU patients, which can persist for years after discharge, with up to 70% of elderly ICU patients experiencing muscle-related complications and a higher mortality rate [7].

3. Risk Factors

A variety of risk factors can lead to the development of ICU neurological and muscular complications, with most identified risk factors coming from clinical observational studies. Some risk factors are related to the primary disease and are unchangeable; others are related to the treatment of the primary disease and are modifiable.

3.1 Sepsis and Multiple Organ Failure

Multiple Organ Failure (MOF) refers to a clinical syndrome where two or more organs fail simultaneously or sequentially after severe infection, trauma, major surgery, or pathological obstetric complications. It is one of the most common risk factors for ICU-AW. The main causes of MOF are sepsis and septic shock. Studies show that over 70% of patients with sepsis will develop ICU-AW as their condition progresses [8]. Research on neurological and muscular complications caused by sepsis dates back to 1892 [9]. Current studies indicate that sepsis can damage the nervous system by releasing key inflammatory mediators such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), leading to sepsis encephalopathy and critical illness polyneuropathy, while also affecting muscle protein metabolism, causing a loss of quantity and quality in skeletal muscle and atrophy, which then progresses to ICU-AW [10]. Sepsis and MOF cause muscle atrophy by affecting mitochondrial function, respiratory chain complex I activity, skeletal muscle ATP levels [11], and tissue oxygen free radical content. Additionally, acute pancreatitis, multiple injuries, and cardiac arrest without sepsis can also lead to MOF resulting in ICU-AW [12].

3.2 Mechanical Ventilation

Mechanical ventilation has been widely used for respiratory support in critically ill patients. However, complications related to mechanical ventilation have also become a major cause of concern for patient outcomes. Only a few studies have focused on the risk factors for respiratory weakness in the ICU. These studies suggest that respiratory muscle weakness is associated with infection or sepsis [13-15], disease severity [15]. The phrenic nerve and diaphragm also exhibit electrophysiological abnormalities similar to those of peripheral nerves and muscles [16], indicating that respiratory weakness is indeed part of ICU-AW [13,15]. Furthermore, the duration of mechanical ventilation may be a factor in diaphragmatic weakness [17,18] and atrophy [18,19]. This time-dependent diaphragmatic atrophy and dysfunction is also known as “ventilator-induced diaphragmatic dysfunction”

(VIDD) [20].

3.3 Braking

Patients who are bedridden for a long period may experience a decline in overall or local physiological functions, potentially leading to complications such as joint contractures, pulmonary infections, pressure ulcers, deep vein thrombosis, constipation, and muscle atrophy. Muscle mass and volume decrease under disuse conditions, with a reduction in the cross-sectional area of muscle fibers and changes in muscle fiber types. The degree of muscle atrophy is related to the duration of disuse and the patient's age [21]. In addition to structural changes in the muscles, the muscle strength of patients with long-term immobilization also significantly decreases. Prolonged inactivity of muscles can lead to mitochondrial dysfunction and an increase in reactive oxygen species (ROS), inducing muscle atrophy and dysfunction [22]. Appropriate resistance training can restore muscle quantity and strength [23].

3.4 Blood Glucose Management

Excessive accumulation of glucose in the body leads to increased inflammatory responses, reduced complement activity, imbalanced immune systems, and mitochondrial damage [24]. Hyperglycemia may cause swelling, degeneration, and necrosis of nerve cells through pathological and physiological mechanisms such as glycogen overload. Patients with hyperglycemia have a 20% increased risk of developing ICU-AW [25]. Hyperglycemia affects respiratory muscle function, resulting in ICU-acquired respiratory muscle weakness and poor prognosis, increasing the mortality rate of patients [26]. Studies have shown that increasing insulin doses can alleviate the signs of ICU-AW [27], therefore, how to ideally control blood glucose levels in ICU patients and conduct predictive assessment and early intervention for ICU-AW is worthy of further research.

3.5 Drug Effects

The correlation between glucocorticoids and neuromuscular blockers with ICU-AW remains controversial. One study found that some ICU-AW is related to the use of glucocorticoids [28], but another multifactorial analysis showed no significant association between glucocorticoids and ICU-AW [29]. Brunello et al. [30] believe that neuromuscular blockers are related to neuromuscular dysfunction, and long-term use of neuromuscular blockers increases the risk of muscle atrophy. However, Papazian et al. [31] showed that the use of neuromuscular blockers did not significantly increase the incidence of ICU-AW. These conflicting research results indicate that the relationship between these drugs and neuromuscular complications is very complex and not determined by a single factor, but also depends on individual differences, dosage and duration of medication, drug interactions, and many other factors.

3.6 Clinical Manifestations and Diagnosis

ICU-AW is primarily characterized by symmetrical weakness in limb muscles, predominantly in the distal parts of the lower limbs, typically without affecting facial and eye muscles. Consequently, during pain reflex testing for ICU-AW patients, changes in facial expressions are often visible, but there is no or only minimal contraction in limb muscles. When ICU-AW occurs, respiratory muscles are frequently affected [32], leading to difficulties in weaning patients from mechanical ventilation. In cases where CIP also occurs, patients may also experience sensory abnormality symptoms, including reduced or absent sensitivity to pain, temperature, and vibration.

Currently, there is no unified standard for the diagnosis of ICU-AW, and guidelines suggest using the Medical Research Council (MRC) score for clinical quantitative assessment of muscle strength in patients [3]. This score rates the activity of 12 muscle groups, including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion, with muscle strength quantified from 0 points (no contraction) to 5 points (full resistance activity), with a total score ranging from 0 to 60. A score of less than 48 or less than 80% of the maximum score (60 points) can be diagnosed as ICU-AW. The scoring is relatively simple and intuitive, but it is overly idealized, and physical examinations of critically ill patients in the ICU are often hindered by the presence of other primary neuromuscular diseases, disorders of consciousness, or sedation and analgesia states. Given the limitations of this diagnostic method, other methods can also be used clinically to diagnose ICU-AW. Muscle electrophysiological changes can be detected 24-48 hours after the onset of ICU-AW, and these changes often occur before clinical symptoms [33]. Electromyography is crucial for the differential diagnosis of clinical subtypes such as CIP and CIM, but electrophysiological testing is not commonly used in clinical practice. Muscle biopsy is the "gold standard" for diagnosing ICU-AW, allowing for a more accurate analysis of the structure and lesion sites of neuromuscular tissues through histomorphology and immunology, to rule out other diagnoses. However, biopsy is an invasive procedure that may lead to complications such as bleeding and infection in routine clinical use [34], and in severe cases, it may even cause neuromuscular dysfunction. Therefore, routine biopsy testing is not recommended in clinical practice.

4. Treatment and Prevention

Due to the incomplete clarity of the pathogenesis of ICU-AW, there are currently no specific drugs or effective treatments available. However, appropriate intervention measures can improve the muscle strength status of patients to some extent, reduce the risk of ICU-AW, shorten hospital stays, and thus improve outcomes. Prevention and early identification of risk groups are crucial.

Active treatment of sepsis is considered the cornerstone of preventing ICU-AW. Rapid identification and active treatment of sepsis and shock are generally considered preventive measures, and targeting newly discovered inflammatory mediators related to muscle atrophy, such as GDF-15, may open up new prospects [35].

Compared to tolerating hyperglycemia up to the renal threshold, insulin therapy aimed at normalizing blood glucose levels significantly reduced the incidence of CIP/CIM electrophysiological signs and shortened the duration of mechanical ventilation in long-term hospitalized ICU patients

[36]. However, other studies [37] indicate that patients receiving strict glycemic control treatment have an increased mortality rate compared to those receiving insulin treatment to achieve higher blood glucose levels. The optimal blood glucose target for ICU patients remains controversial, and efforts are currently being made to explore a safer range for blood glucose control in ICU-AW patients.

ICU patients often have prolonged bed rest, hence reducing immobilization time and early rehabilitation therapy are important measures to prevent ICU-AW. Lowering the level of sedation and using the minimum dose of sedatives necessary to keep patients comfortable and safe can help reduce immobilization time. A study has shown that early functional exercise contributes to the recovery of muscle strength in critically ill patients, thereby reducing the incidence of ICU-AW [38]. Tipping et al. concluded that active activities and rehabilitation therapy can improve muscle strength in ICU patients at discharge, increase the likelihood of being able to walk without assistance at discharge, and extend survival and non-hospitalization time within 180 days after discharge [39]. In addition, for patients who are unable to cooperate with active rehabilitation therapy and exercise, neuromuscular electrical stimulation (NMES) has been suggested as an alternative. This method primarily stimulates skeletal muscles in a state of disuse with low-frequency currents, enhancing motor nerve and muscle contractility, achieving the effect of delaying or even reversing muscle atrophy [40]. This treatment has been proven to increase muscle strength and exercise tolerance in non-ICU populations [41], and its use in ICU patients is worth further investigation.

5. Summary

Given the profound impact of ICU-AW on the prognosis of ICU patients, its risk factors, diagnostic methods, and treatment remain hot topics of current research. ICU-AW prevention and treatment measures are abundant, and early identification and management of risk factors can help mitigate the severity of ICU-AW and improve outcomes. In addition, there are more treatment methods worth further exploration.

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