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Generalized Weakness in Intensive Care Unit: Review Article

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Abstract **Background:** Muscle weakness is common in the surgical intensive care unit (ICU). Low muscle mass at ICU admission is a significant predictor of adverse outcomes. The consequences of ICU-acquired muscle weakness depend on the underlying mechanism. Severe perioperative acquired weakness that is associated with adverse outcomes (prolonged mechanical ventilation, increases in ICU length of stay, and mortality) occurs with persistent (time frame: days) activation of protein degradation pathways, decreases in the drive to the skeletal muscle, and impaired muscular homeostasis. **Methods**: In this article, we review the current state-of-the-art of the basic pathophysiology of nerve and muscle weakness after critical illness and explore the current literature on ICUAW with a special emphasis on the most important mechanisms of weakness. In addition to review our understanding of the molecular pathogenesis of ICUAW in the context of current knowledge of clinical risk factors and etiology. **Results:** ICU-AW can be caused by a critical illness polyneuropathy, acritical illness myopathy, or muscle disuse atrophy, alone or in combination. Its diagnosis requires both clinical assessment of muscle strength and complete electrophysiological evaluation of peripheral nerves and muscle **Conclusion:** ICU-AW can be prevented by early treatment of the underlying disease, goal-directed therapy, restrictive use of immobilizing medications, optimal nutrition, activating ventilatory modes, early rehabilitation, and preventive drug therapy.

Keywords: *muscle weakness, ICU-acquired weakness*

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1. Introduction

ICU-AW presents a severe and frequent complication of critical illness, confronting intensivists around the globe with various difficulties. It is believed that ICUAW can affect more than half of all ICU patients. This substantial neuromuscular complication of critical illness is associated with increased rates of morbidity and mortality, substantially affecting both short- and long-term clinical outcomes in septic patients [1].

MUSCLE weakness occurs as frequently as low arterial blood pressure in the intensive care unit (SICU). The incidence of sarcopenia (low skeletal muscle mass) in the intensive care unit (ICU) can be as high as 70% depending on the age, presentation, and comorbidities of the patient, and preexsiting sarcopenia predicts adverse discharge disposition. Muscle mass decreases by approximately 2% per day as a consequence of patients' acute disease and their ICU treatment [2].

Intensive care unit acquired weakness (ICU-AW) is the most common neuromuscular impairment in critically ill patients.

We discuss critical aspects ofICUAW that have not been completely defined or that are still underdiscussion. Critical illness polyneuropathy, myopathy, and muscle atrophycontribute in various proportions to ICUAW. Diagnosis of ICUAW is clinicaland is based on Medical Research Council sum score and handgripdynamometry for limb weakness and recognition of a patient's ventilatordependency or difficult weaning from artificial ventilation for diaphragmaticweakness [3].

The main determinants of endurance are the maximal oxygen uptake and the rate of glycogen depletion. Lack of endurance promotes a reduction in the exercise-induced capacity to generate force over time, which is known as muscle fatigue. Muscle fatigue can be classified, based on

the evoked response to repeated muscle stimulation, into two types: low-frequency fatigue (relative loss of force at low frequencies of stimulation and a slow recovery over the course of hours or even days) and high-frequency fatigue (excessive loss of force at high frequencies of stimulation and rapid recovery when the frequency is reduced).Fatigue and deficits in endurance impair muscle performance leading to lack of muscle strength or dynapenia [4].

The muscles of patients with ICUAW demonstrate a range of alterations. Muscle strength depends on the force-generating capacity of the muscle and the muscle mass, and both are thought to be affected in ICUAW. Clinically, this manifests as muscle wasting preceded by abnormal muscle electrophysiology [5].

2. Review

ICUAW is a frequent problem. The reported incidence varies depending on the patient population studied and on the timing of the evaluation. Weakness was found to be present in 26-65 % of patients who were mechanically ventilated for 5-7 days, respectively, and 25 % of these remained weak for at least another 7 days after awakening [6]. Among long-term ventilated patients (≥10 days) ICUAW was diagnosed in up to 67 %. In patients suffering from a cute re spiratory distress syndrome (ARDS), an ICUAW incidence of 60 % has been reported at the time of awakening, and at hospital discharge this incidence was still 36 % [7].

3. Mechanism of ICUAW

Normally, skeletal muscle exists in a regular striated pattern, formed by the organisation of the myofilaments, which is required for the generation of force in an organised manner. In the muscle of patients with ICUAW, there is a significant disruption to this organisation, which is likely to contribute to the reduction in the force-generating potential of the muscle. As seen in muscle wasting associated with ageing and other atrophic states, such as chronic inflammation or starvation, a shift towards fast fibres expressing type 2 myosin has been reported in ICUAW (Figure 1). In addition, these type 2 fibres demonstrate greater atrophic changes and are thought to waste more rapidly, suggesting increased sensitivity of type 2 fibres to the multifactorial insult of critical illness [8].

Other mechanisms that contribute to the loss of power include neuropathy, a reduction in energy generation by the muscle through insulin resistance and mitochondrial dysfunction, dysregulation of calcium handling and electrical inexcitability. Protein degradation occurs through a number of pathways, including the ubiquitin–proteasome (UP) pathway, caspase and calpain activity, and autophagy. Of these, the UP pathway is thought to be the major mechanism of proteolysis [9].

4. Causes of Intensive Care Unit Weakness

ICUAW is characterised by skeletal muscle wasting and weakness. In severe cases, complete paralysis can occur and up to 30% of patients are left with long-term disability. ICUAW is associated with failure to wean from mechanical ventilation, increased length of stay in the intensive care unit (ICU) and hospital, and in some studies with increased risk of death. At least 25% of patients who are intubated for more than 7 days develop ICUAW as do up to 100% of those who have severe sepsis and systemic inflammatory response syndrome [10].

5. Sub Classification of ICUAW

Depending on electrophysiologic or histological documentation of neuropathy and/or myopathy, ICUAW can be further subclassified as critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or critical illness myoneuropathy (CIMN), which is more frequent than previously thought and applies to ICUAW patients with coinciding neuropathy and myopathy. Myopathy is likely to present the predominant feature of ICUAW and has been shown to precede neuropathy in patients with CIMN [3].

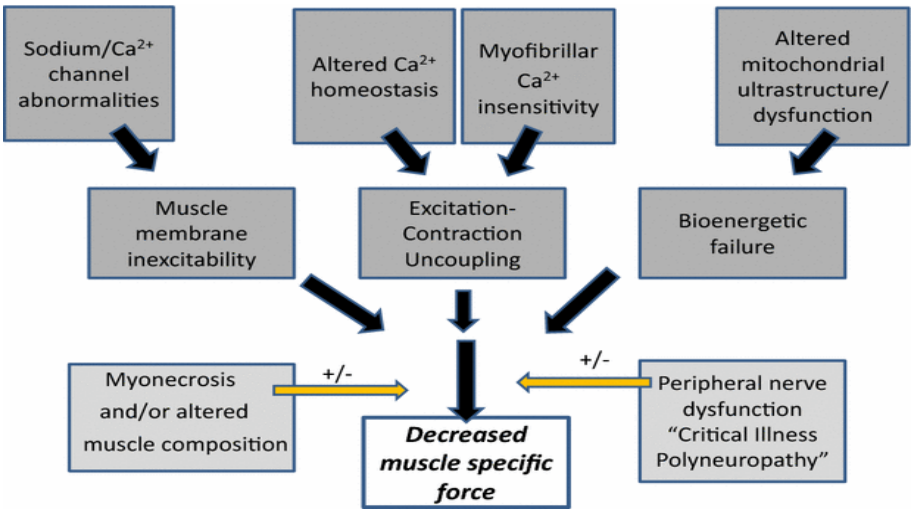

Figure 1. Impaired muscle contractility in critical illness [12]

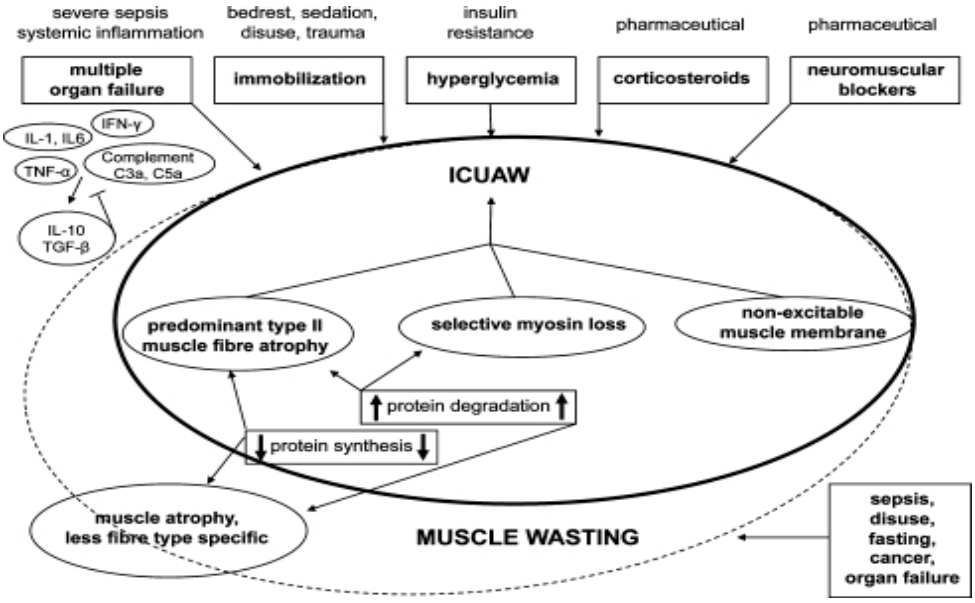

Figure 2. Risk factors involved in muscle wasting and ICUAW [11]

6. Risk Factors Involved in ICUAW

While the exact molecular mechanisms contributing to ICUAW remain to be elucidated, five central risk factors of ICUAW have been repeatedly reported (Figure 2) [11].

Sepsis, systemic inflammatory response syndrome, and mul-tiple organ failure are important risk factors for the develop-ment of ICUAW [6]. Hyperglycemia is an independent risk factor for ICUAW; thus, controlling glycemia through intensive insulin therapy and early mobilization can decrease ICUAW, which is also elective for reducing the duration of mechani-cal ventilation. Because long-term immobilization and mechanical ventilation can cause severe limb muscle atrophy, it is necessary to reduce the duration of immobilization by en-suring early mobilization [13]. The effects of using corticoste-roids and neuromuscular blocking agents in critically ill pa-tients with ICUAW are controversial, and they are expected to affect complex pathways in ways that depend on factors such as dose, timing, glycemic control, and neuromuscular com-plications [3,9]. Age is an independent risk factor for ICUAW, and premorbid physiological muscle reserve may play an im-portant role. Decreased skeletal muscle mass at the time of ICU admission is another important risk factor for mortality and complications, and this factor merits particular consider-ation in elderly patients [14].

7. Clinical Presentation of ICUAW

ICUAW is characterized by symmetrical and flaccid weakness of the limbs, which is more pronounced in the proximal muscles than in the distal muscles. Facial and ocular muscles are often spared. Patients with ICUAW therefore typically respond to a painful stimulus with facial grimacing but with no or minimal with drawal of the limbs. Tendon reflexes are generally reduced, although these can be normal. In the case of coexistent CIP, sensory symptoms may be present, including reduced or absent sensitivity to pain, temperature, and vibration. However, examination of the sensory function is generally difficult in critically ill patients. When ICUAW is present, the respiratory muscles are often affected. This contributes to delayed weaning from mechanical ventilation, which is often the clinical problem with which these patients present [15].

This primarily affects the lower limbs but may extend to tetraplegia in more severe cases, explaining its prior terminology of acute quadriplegic myopathy. Whenever suspecting ICUAW, it is fundamental to rule out prolonged neuromuscular blockade (involvement of cranial nerve-innervated muscles), pre-existing neuromuscular dysfunction and other conditions as alternative causes [16].

8. Diagnosis of ICUAW

Weakness is common after an episode of critical illness and its associated disability may persist for years, with significant negative impact on the survivor. Strength depends on both the presence and normal function of skeletal muscle, so that either muscle wasting or impaired contractility (muscle-specific force) can induce weakness. Therefore, studies evaluating ICU-acquired weakness (ICUAW) should ensure complete assessment for peripheral neuropathy, neuromuscular junction dysfunction in addition to evaluation for myopathy—loss of muscle mass and deficiency of intrinsic contractility [12]. The diagnosis of ICUAW is confirmed via clinical features, and predisposing factors based on a physical examination and causes other than critical illness should be excluded. Performing an accurate physical examination is difficult, and in patients showing slow recovery after severe muscle weakness, an electrodiagnostic evaluation can be considered [13].

9. Electrophysiologic Testing

An electrodiagnostic evaluation, such as a nerve conduction study (NCS) or electromyography is necessary to diagnose CIP and CIM, and direct muscle stimulation

can be additionally used to distinguish between CIP and CIM In NCSs, nerve conduction velocity is mostly normal, while the amplitude of compound muscle action potentials (CMAPs) is reduced [17]. It offers an additional approach to estimate neuromuscular dysfunction in unconscious patients incapable of voluntary contraction Table 1. Moreover, electrophysiologic testing after direct muscle stimulation can be conducted in unconscious/sedated patients and has been shown to predict ICUAW with high sensitivity and specificity in mechanically ventilated, sedated patients and differentiates between primary nerve or muscle dysfunction [18].

10. Manual Muscle Testing

A clinical diagnosis of ICUAW can be made through a bedside evaluation of muscle strength. The Medical Research Council (MRC) scale is used for manual muscle testing. It assesses the strength of the muscle groups of the upper and lower limbs, and an MRC sum score of less than 48 out of 60 points indicates an ICUAW diagnosis .A diagnosis of frailty can be made by using validated instruments for assessment of mobility, muscle mass, nutritional status, strength, and endurance are all valid identifiers of clinically weak patients. Earlier detection of ICUAW is possible and can be obtained by assessment of voluntary maximum strength in ICU patients, either by hand dynamometry or according to the Medical Research Council (MRC)-score [3].

The MRC-score grades manually tested strength from 0 (no movement observed) to 5 (muscle contracts normally against full resistance) in three functional muscle groups of each extremity, with mean MRC-scores of <4 (antigravity strength) indicating ICUAW. It has shown good interobserver reliability in patients with Guillan-Barré syndrome. Values of <11-kg force for men and <7-kg force for women at dominant-hand dynamometry have also been described to identify ICU-acquired weakness in previously healthy individuals [19].

Among other methods of muscle testing, the use of handheld dynamometry and handgrip dynamometry can be considered (Figure 3). Both methods are good to excellent in terms of interrater reliability and must be applied in patients who are at least grade 3 on the MRC scale . In addition, it is necessary to ensure that the patient remains in a consistent position, including limb positions, joint angles, and hand position of the tester, and it is also necessary to standardize the contraction time, number of repetitions, and rest periods between tests [20].

Respiratory muscle strength can also be evaluated in patients with ICUAW. Maximum inspiratory pressure can be used to assess inspiratory muscle strength, and the unidirectional valve method can be used for an accurate assessment, from which the possibility of success of weaning can be predicted. Moreover, direct measurements of muscle strength, ultrasound can be used to assess muscle thickness and ultrasonic echogenicity, thereby serving as a straightforward method to detect changes of muscle mass in critically ill patients [21].

Table 1. Diagnosis of ICUA [18]

Condition	Definition	Diagnosis
Intensive care unit–acquired weakness (ICU-AW)[1,2]	Clinically detected, diffuse, symmetric weakness involving all extremities and respiratory muscles arising after the onset of critical illness	c) Medical Research Council (MRC) sum score of less than 48/60 or mean MRC score of 4 in all testable muscle groups d) Dominant-hand handgrip dynamometry scores of less than 11 kg (interquartile range (IQR) 10–40) in males and less than 7 kg (IQR 0–7.3) in females
Diaphragmatic weakness (DW)[9]	Reduced pressure-generating capacity of the diaphragm and a decreased diaphragm thickness and thickening fraction after initiation of mechanical ventilation	d) Endotracheal tube pressures less than 11 cm H_2O after bilateral phrenic nerve magnetic stimulation during airway occlusion e) Diaphragm excursion at muscle ultrasound less than 11 mm during tidal breathing f) Diaphragm thickening fraction at muscle ultrasound less than 20%
Critical illness polyneuropathy (CIP)[1]	An axonal, sensory-motor polyneuropathy with reduced nerve excitability and loss of axons with preserved myelin sheet	Reduced amplitude of compound muscle action potentials and sensory nerve action potentials with normal or mildly reduced nerve conduction velocity on electroneurography
Critical illness myopathy (CIM)[1]	A primary acute myopathy with reduced muscle membrane excitability and loss of myosin filaments, fiber atrophy, and necrosis	Reduced amplitude of compound muscle action potentials and normal sensory nerve action potentials on electroneurography and reduced muscle excitability on direct muscle stimulation and myopathic motor unit potentials on needle electromyography
Combined critical illness polyneuropathy and myopathy (CRIMYNE)[1]	Combined CIP and CIM	Reduced amplitude of compound muscle action potentials and sensory nerve action potentials combined with myopathic features on needle electromyography

Figure 3. Assessment of muscle strength with a handgrip dynamometer (A) and handheld dynamometry [20]

11. Treatment Options

11.1. Treatment of Sepsis

In addition to the optimum realization of early goal-directed sepsis therapy, there are a number of hypothetical approaches targeting inflammation-mediated multiple organ failure, such as reducing levels of distinct cytokines by extracorporeal measures, or restoring the immunological equilibrium by pharmaceutical immunomodulation [22].

11.2. Early Mobilization

Schweickert and colleagues recently reported that patients undergoing an ambitious protocol of early and determined mobilization were more frequently able to get out of bed, stand and occasionally walk with assistance during mechanical ventilation whereas standard regimens of physical therapy led to longer impairment of functional status and recovery time [23]. Besides, early mobilization was associated with a shorter duration of delirium. It is possible, that additional electrical muscle stimulation (EMS) assists in preventing ICUAW, since studies indicate that EMS partially prevents muscle atrophy in critically ill patients and mitigates increased proteasome activation besides stimulating insulin like growth factor in patients after major abdominal surgery (Figure 4) [24].

11.3. Intensive Insulin Therapy

Increased serum glucose levels are typical findings in patients with severe sepsis and septic shock. Studies from van den Berghe and colleages reported that intensive insulin therapy (IIT) was associated with a lower incidence of ICUAW [25]. Insulin therapy alleviates the catabolic syndrome of prolonged critical illness because of its well-recognized anabolic properties, comprising stimulation of muscle protein synthesis and attenuation of protein breakdown. In addition, mortality rate is significantly lower in critically ill patients with liberal glycemic control (serum glucose ≤180 mg/dl),and Patients who received intensive insulin therapy were less likely to develop CIPNM (29%) than were those receiving conventional treatment (52%) [26].

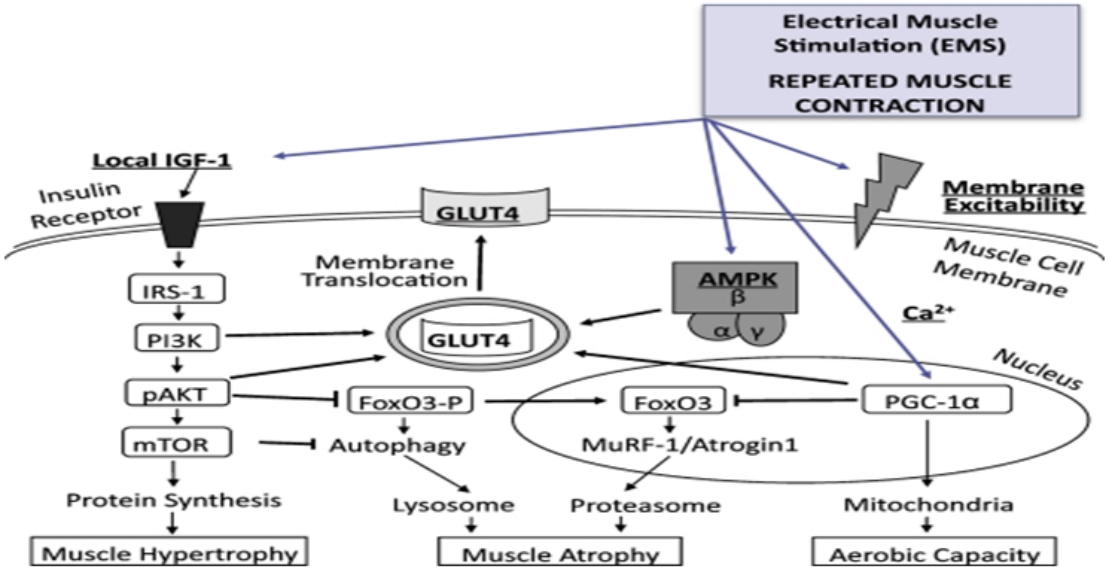

Figure 4. Beneficial effects of electrical muscle stimulation (EMS) [24]

11.4. Glucocorticoid Exposure

A variety of therapies may prevent the development of ICU-acquired weakness, Neuromuscular blocking agents and corticosteroids often are avoided to decrease the risk of ICU-acquired weakness, de Jonghe et al. identified corticosteroid administration as the strongest predictor for ICU-acquired weakness, development of steroid induced myopathy may be dependent on steroid doses applied, strict indication is still warranted considering low-dose hydrocortisone administration [25].

11.5. Neuromuscular Blockers

Treatment with neuromuscular blocking agents has been reported to contribute to ICUAW development. Initial reports stated that vecuronium and pancuronium may be particularly harmful in regard to critical illness neuromuscular abnormalities [27].

Because poor alertness and cooperation precludes early active mobilization of a large proportion of patients, neuromuscular electrical stimulation (NMES) has been suggested as an alternative.Several mostly small RCTs have been performed in critically ill patients, with vari-able use of frequencies, intensities and duration of NMES and widely varying outcomes, limiting pooling and inter-pretation of data [28].

11.6. Sedation Prevention

Sedative agents may mask symptoms or delay identification of ICU-acquired weakness by clinicians. In general, the use of daily interruption of sedative agents and limiting the administration and dosing of sedative agents improve the outcome of patients who are critically ill and improve the clinician's ability to diagnose ICU-acquired weakness at an earlier time point [29].

Ouimet et al reported ICU delirium was linked to longer length of stay in both the ICU and hospital, as well as increased mortality for both. Hopkins and Jackso reviewed studies that evaluated neurocognitive outcomes following critical illness and found that associated cognitive changes negatively affected daily physical function, quality of life, and return to work [30,31].

12. Conclusion

Clinical analysis of muscle function should become a regular part of clinical examination in the ICU to allow appropriate identification and management of muscle weakness to prevent long-term morbidity and mortality and reduce healthcare costs. ICUAW weakness is a direct consequence of the patient’s systemic disease and its treatment. Aggressive treatment of the underlying disease is a key strategy to its prevention. Muscular inactivity and excessive load need to be prevented, and a metabolic environment that allows for optimal recovery should be created. In addition identification of risk patients, avoidance of unnecessarily deep sedation, promotion of early mobilisation and EMS, prevention of excessive blood glucose levels, rational administration of glucocorticoids and/or neuromuscular blockers as well as early goal-directed therapy of sepsis seem to reduce the severity and incidence of ICUAW.

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