Intensive care unit-acquired weakness: Questions the clinician should ask.

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Abstract

Intensive care unit (ICU)-acquired weakness (ICU-AW) is defined as clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. Using electrophysiological methods, patients with ICU-AW are classified in three subcategories: critical illness polyneuropathy, critical illness myopathy and critical illness neuromyopathy. ICU-AW is a frequent complication occurring in critical ill patients. Risk factors include illness severity and organ failure, age, hyperglycemia, parenteral nutrition, drugs and immobility. Due to short- and long-term complications, ICU-AW results in longer hospital stay and increased mortality. Its management is essentially preventive avoiding modifiable risk factors, especially duration of sedation and immobilization that should be as short as possible. Pharmacological approaches have been studied but none have proven efficacy.

In the present review, we propose practical questions that the clinician should ask in case of acquired weakness during ICU stay: when to suspect ICU-AW, what risk factors should be identified, how to diagnose ICU-AW, what is the prognosis and how can recovery be improved?

Keywords: ICU-acquired weakness; Critical illness polyneuropathy; Illness severity; Delayed weaning; Neurophysiology.

INTRODUCTION

Intensive care unit (ICU)-acquired weakness (ICU-AW) is defined as clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness [1]. Using electrophysiological methods, patients with ICU-AW are classified in three subcategories: critical illness polyneuropathy (CIP), critical illness myopathy (CIM) and critical illness neuromyopathy (CINM) [1]. The involvement of the neuromuscular junction is also possible, mainly related to residual neuromuscular blockade [2]. ICU-AW is a frequent complication occurring in critical ill patients with risk factors including illness severity and organ failure, age, hyperglycemia, parenteral nutrition, drugs and immobility [3]. Due to short- and long-term complications, ICU-AW results in longer hospital stays and increased mortality [3].

In the present review, we propose practical questions that the clinician should ask in case of acquired weakness during ICU stay: when to suspect ICU-AW, what risk factors should be identified, how to diagnose ICU-AW, what is the prognosis and how can recovery be improved.

1. WHAT ARE THE EXPLANATIONS OF ICU-ACQUIRED WEAKNESS?

ICU-AW may involve any part of the neuromuscular system (**Fig. 1**): the peripheral nerves leading to CIP, the neuromuscular junction leading to critical illness neuromuscular blockade (CNMB), and the muscle leading to CIM [1].

Critical illness polyneuropathy. CIP may involve all three types of neurons running in the peripheral nerves, namely (1) motor neurons, (2) large sensory fibers, and (3) small fibers (**Fig. 1**). These three types of neurons have different functions and can be involved or not in a same patient, leading to different presentations from isolated weakness to sensory involvement. Therefore, CIP results in a variable combination of the following clinical symptoms and signs:
(1) As peripheral motor neurons innervate the muscles and participate in the deep tendon reflex arc, their involvement therefore leads to muscle weakness, atrophy and hypotonia affecting symmetrically the four limbs with a lower limb and distal predominance, sparing the facial and ocular muscles; reduced tendon reflexes; and possible respiratory muscle weakness resulting in prolonged mechanical ventilation (MV) and delayed weaning.
(2) Large sensory nerve fibers carry information about touch, vibration and proprioception and participate in the deep tendon reflex arc, their involvement therefore leads to reduced touch, vibration and proprioception sensations, neuropathic pain and reduced deep tendon reflexes.

These signs mainly affect distal part of the limbs (“stockings” and “gloves” pattern) but can affect any part of the body.

(3) Small nerve fibers carry pain and temperature information and contribute to the autonomic system. Their involvement leads to moderate manifestations (orthostatic hypotension, abnormal heart rate variation, vasomotor disorders), prominent dysautonomia being exceptional, reduced temperature and pain sensations and neuropathic pain mainly affecting distal part of the limbs (“stockings” and “gloves” pattern) but any part of the body can be affected [4,5].

In CIP, electrodiagnosis (EDX) study of motor and large sensory fibers most frequently reveals acute and ongoing axonal sensorimotor polyneuropathy usually within one to three weeks after ICU admission. Nerve conduction studies (NCS) show low amplitudes with relatively preserved nerve conduction velocities and distal latencies. Electromyography reveals fibrillation potential at rest in almost all patients and decreased recruitment of motor unit action potentials (MUAPs). At the onset of CIP, MUAPs have a normal morphology then, secondarily to reinnervation, a long duration weeks to months after the onset of CIP [6–8]. Muscles from the limbs should be systematically studied, but phrenic EDX can also be performed in case of delayed weaning. As EDX only explores motor and large sensory fibers, isolated small fiber involvement results in normal NCS, and requires other tools such as abnormal sympathetic skin responses or decreased small fiber density highlighted in skin biopsies [4,5]. Nerve biopsies display primary distal axonal degeneration of motor and sensory fibers [9–11].

Critical illness myopathy. CIM results in muscle weakness and atrophy affecting symmetrically the four limbs with proximal predominance but sparing the face and ocular muscles. Usually, there is no sensory dysfunction nor reduced deep tendon reflexes (unless there is coexisting CIP). Respiratory muscle weakness can also be observed, with prolonged MV and delayed weaning [12]. Most frequently, EDX reveals a typical myogenic pattern in CIM: NCS can show low amplitudes when studying motor nerves with normal sensory examination; electromyography can reveal fibrillation potential at rest in 70% of patients, and MUAPs of short duration and low amplitude with early full recruitment [7]. Creatine kinase levels may be elevated but can also be in the normal range [13]. Muscle biopsy reveals myofiber atrophy, thick filaments (myosin) loss and muscle necrosis [14,15].

Critical illness neuromuscular blockade. Neuromuscular junction involvement in relation with critical illness has been demonstrated [2]. Descriptions of CINMB, especially two to 10 days after cessation of nondepolarizing neuromuscular blocking agents, have been

described as transient flaccid areflexic weakness affecting symmetrically the four limbs, the face and the ocular muscles (ptosis, ophthalmoparesis), without sensory dysfunction. EDX reveals decremental response during repetitive nerve stimulation [16].

Even though CIP, CINMB and CIM may have different clinical features (e.g. CIP manifestations being more distal and associated with sensory symptoms and areflexia compared to CIM), their main manifestations clearly overlap (symmetrical flaccid weakness affecting limb and respiratory muscles) and they are frequently associated in a same patient [17,18]. Moreover, clinical and EDX explorations can be difficult because of insufficient patient cooperation due to sedation or encephalopathy, and the use of nerve; use of muscle biopsies is limited as they are invasive procedures. Therefore, in clinical practice and in studies, it may be difficult to differentiate CIP, CINMB and CIM.

2. WHY DO SOME PATIENTS DEVELOP ICU-AW?

Pathophysiology of ICU-AW. The pathophysiology of ICU-AW remains partially understood [19,20]. Skeletal muscle function has been mainly studied during sepsis. A recent review summarizes two major events leading to ICU-AW: muscle atrophy and muscle dysfunction [3]. Muscle atrophy is related to neuroendocrine alterations with an imbalance between increased catabolism and decreased anabolism [21]. Furthermore, extended bed rest in ICU, contributing to loss of muscle mass with immobilization, disuse, unloading and sometimes MV, could favor functional denervation [22,23]. Muscle wasting occurs early and rapidly during the first week of critical illness, especially among patients with multiple organ failure [23]. In other ways, muscle dysfunction is associated with energetic failure due to microcirculatory changes and mitochondrial dysfunctions [24]. Skeletal muscle biopsies in septic patients showed overproduction of nitric oxide, antioxidant depletion, mitochondrial dysfunction and decreased ATP concentration, implicating bioenergetic failure [25]. In a mouse model of sepsis, muscle was not able to regenerate after sepsis. Satellite cells, which play a key role in muscle homeostasis and regeneration, were impaired; mitochondrial bioenergetic failure could contribute to these alterations [26]. Changes in membrane and ion channel function could contribute to disturbed excitation-contraction coupling [24]. Muscular inexcitabilty can be explained by a modification of the properties or the type of voltage-gated sodium channels, with an up-regulation of the NaV 1.5 sodium channel [27]. Accumulation of damaged organelles and proteins results in insufficient autophagy [24]. These modifications in cellular physiology contribute to alterations in muscle structure and muscle function [15].

Risk factors of ICU-AW. Risk factors have been identified and are usually separated according to whether they appear to be modifiable or not [3,28]. The main risk factors are presented in **Table 1** [17,22,28–41]. Concerning the impact of drugs, data are uncertain [3]. The use of neuromuscular blocking agents may contribute to ICU-AW, probably in combination with other risk factors related to critical illness severity (e.g. sepsis, multiple organ failure) [32–34]. Corticosteroids may increase the risk of ICU-AW, especially during sepsis [17,35,36]. Aminoglycosides and the use of vasoactive medications could also promote ICU-AW [28,37]. To conclude, the use of these drugs should be limited if possible in time, especially when they are combined in a context of organ failure (e.g. acute respiratory distress syndrome).

3. HOW TO DIAGNOSE ICU-AW?

Diagnostic criteria have been proposed for ICU-AW and its three subcategories (CIP, CINMB and CIM), considering clinical findings such as limb weakness, abnormal EDX, and abnormal muscle biopsy for CIM [1,42]. Even though these criteria have the major advantage of filling the lack of consistent nomenclature, their application is difficult in clinical practice. First, EDX and muscle biopsy are not accessible for 25 to 45% of patients who may be concerned by ICU-AW [43]. Moreover, the use of muscle biopsy to diagnose CIM may raise ethical issues, as it is an invasive procedure and may not change patient management. Finally, many patients with ICU-AW do not fulfill these criteria, e.g. sedated patients in whom a weakness cannot be highlighted, or patients with compound muscle action potentials which significantly decreased during ICU-stay but remained up to 80% of the lower limit of normal [4].

Latronico and Bolton have already proposed a diagnostic algorithm [42]. We here propose an easy diagnostic procedure usable in clinical practice, based on the idea that ICU-AW is secondary to any neuromuscular abnormality acquired during critical illness and without any plausible etiology other than critical illness itself. Therefore, clinical or paraclinical manifestations should fulfill three criteria to suspect ICU-AW:

(1) Manifestations should be related to a neuromuscular abnormality,
(2) Manifestations should have been acquired during critical illness, without evidence of prior presence,
(3) Manifestations should not be explained by any plausible etiology other than critical illness.

First, is the manifestation a neuromuscular abnormality? Clinical signs should be better explained by neuromuscular involvement (see question 1) rather than central nervous system or other organ dysfunction. For example, weakness lateralized to one side of the body (hemiplegia), associated with seizures or with cognitive dysfunction orients toward a central nervous system lesion; difficulty in weaning can be related to cardiac or pulmonary involvement. In doubtful situations, paraclinical examinations are indicated to confirm neuromuscular involvement (e.g. EDX, creatine kinase blood levels or muscle/nerve biopsies) or to check for the possibility of another system dysfunction (e.g. brain or spinal cord magnetic resonance imaging, echocardiography, chest computed tomography). When abnormal paraclinical examinations are compatible with a neuromuscular abnormality, such as EDX displaying sensory motor axonal polyneuropathy or abnormal muscle on biopsies, the clinician should consider the possibility of artifacts or technical issues, especially if they are weakly correlated with clinical findings.

Secondly, was this neuromuscular abnormality acquired during critical illness? Any evidence that the considered neuromuscular manifestation is older than the critical illness should raise the possibility of a differential diagnosis. Careful history taking from the patient and/or family can provide useful evidence (e.g. limb atrophy or weakness which was present before the critical illness), as can physical examination at admission (e.g. decreased deep tendon reflex due to probable preexisting peripheral neuropathy) or when performing EDX (e.g. large and long muscle action potentials related probable chronic and therefore preexisting peripheral neuropathy). History, complete neurological examination at admission, and precise analysis of potential EDX data are needed to check this second criterion. When a preexisting neuromuscular disorder is present, ICU-AW can appear and lead to worsening of the clinical manifestation. Weighting the impact of ICU-AW in this situation, may be challenging.

Finally, can this neuromuscular abnormality be explained by another etiology than critical illness? As ICU-AW is frequent, intensivists should recognize these typical presentations, i.e. moderate flaccid bilateral symmetrical weakness sparing the cranial nerves and atrophy of neuromuscular origin acquired during critical illness. Nevertheless, in case of severe and/or atypical manifestations, e.g. facial and oculomotor involvement, the patient should be referred to neuromuscular experts who will check for differential diagnoses. For example, in case of wrist drop, which is not a typical presentation of ICU-AW, the intensivist should call in the neuromuscular expert, with immobilization-related radial nerve compression

a probable conclusion. In case of prolonged difficult weaning or severe four-limb weakness (quadriplegia), the intensivist should also call in the neuromuscular expert, who will probably complete the examination with EDX to look for differential diagnoses (e.g. demyelination which may suggest a Guillain-Barré syndrome). Even with a typical presentation of CIP and CIM, it can be worthwhile to look for frequent neuromuscular disorders, which may be differential diagnoses or even associated conditions. For example, since peripheral neuropathy is frequent in the general population (2-7% of the worldwide population) [44], it may be reasonable to include systematic first-line explorations for peripheral neuropathies – blood glucose and/or hemoglobin A1c, serum protein immunofixation electrophoresis, vitamin B12, homocysteine or methylmalonic acid, thyroid stimulating hormone (at least for CIM) – in the CIP diagnostic work-up.

Weakness should be monitored regularly. Quantifying tools, e.g. the MRC-sumscore, a summation of the strength of six muscle groups tested on both sides, can be useful (**Table 2**) [45]. Sumscores range from 0 (tetraplegia) to 60 (normal strength).

4. HOW CAN RECOVERY FROM ICU-AW BE IMPROVED?

Prognosis. ICU-AW patients require a longer duration of MV [12,17,32,40,46]. They have a higher risk of extubation failure [12,46,47] and swallowing disorders [48].

Conventional extubation attempts follow successful spontaneous breathing trials and positive results for ventilator weaning parameters, otherwise patients undergo tracheostomy [49,50]. The respiratory component of ICU-AW has been investigated and found to contribute to difficulty in weaning from the ventilator and to prolonged duration of MV [12]. The authors proposed to assess respiratory function using bedside measurements in ICU awakening patients after seven days of MV [12]. They measured maximal inspiratory (MIP) and expiratory pressure (MEP) and vital capacity (VC) via the tracheal tube during a short disconnection from the ventilatory circuit and found that alterations of these variables were associated with limb weakness severity [12]. Low MIP (≤30 cm H_2O), low MEP (≤30 cm H_2O) and MRC score were predictors of delayed extubation and prolonged MV [12]. However, using a spirometer at the ICU bedside after awakening can generate anxiety and contribute to immediate poor respiratory tolerance [12]. Low MIP (≤30 cm H_2O) is also an independent risk factor for one-year mortality in ICU patients requiring MV [51]. Assessing the severity of the respiratory component could be useful to guide weaning from MV and the indication for tracheostomy. Tracheostomy should be proposed in case of prolonged MV or extubation failure and discussed when delayed extubation is expected. However, the exact timing for tracheostomy and its impact on MV

duration are uncertain. Using noninvasive MV and mechanically-assisted coughing could contribute to safe extubation of unweanable patients [49].

These acute complications lead to higher ICU and hospital mortality [32], longer ICU and hospital length of stay [37,46] and increase in-hospital cost. However, ICU-AW is often reversible with a median three-week delay before recovery [17]. Recovery may be incomplete [52,53] and depend on the electrophysiological subtype. Indeed, some studies have suggested worse prognosis of recovery in CIP compared to CIM [54,55].

ICU-AW is a part of the post-ICU syndrome, which includes several manifestations such as posttraumatic stress disorder, anxiety and depression [56].

Management of ICU-AW. Management of ICU-AW is summarized in **Figure 2** and remains mainly preventive. Currently, there is no specific treatment and the choice of appropriate management practices will require a better understanding of the underlying pathophysiology [19]. Some interventions have been proposed but poorly studied [3,57]:

- *Early treatment of sepsis*. Considering organ failure, sepsis and illness severity are the main risk factors (cf. question 2). Early treatment could contribute to decreased risk of ICU-AW, according to guidelines [58].

- *Avoiding hyperglycemia*. Two large trials provide evidence that intensive insulin therapy (blood glucose levels less than 110 mg/dl) reduces the risk of both CIP and CIM, and could contribute to reduce the duration of MV, ICU stay and 180-day mortality [29–31]. Recently, a study concerning Guillain-Barré syndrome found that dysglycemia might have an impact in functional outcome and suggested that blood glucose control might be an adjuvant therapy [59].

- *Limiting early parenteral nutrition*. Nutritional management in the ICU is partially understood. Concerning the risk of ICU-AW, parenteral nutrition could have a negative impact, and enteral nutrition should be preferred [60]. Interestingly, obesity seems to be protective regarding the risk of ICU-AW, probably due to the availability of ketone bodies [61].

- *Minimizing sedation and early mobilization*. Sedative drugs could have a direct impact on ICU-AW genesis [22]. It seems important to decrease the use and the duration of sedation and MV to promote early mobilization and prevent the occurrence of diaphragm dysfunction [62]. Diaphragm dysfunction contributes to a longer duration of MV, which is itself a risk factor of ICU-AW [12].

- *Drugs*. Several pharmacological interventions, e.g. myostatin inhibitors, have been studied but none are recommended for routine use [57,63]. In another way, some drugs could

promote ICU-AW and their use must be rationalized, e.g. neuromuscular blockade agents, corticosteroids.

- *Early rehabilitation during the ICU stay*. Early rehabilitation could contribute to shorter duration of MV but has no demonstrated effect on ICU length of stay [30,64].

- *Rehabilitation beyond the ICU stay*. There are no published randomized controlled trials that examine whether physical rehabilitation interventions improve activities of daily living for people with CIP and CIM [65].

- *Electrical muscle stimulation*. There is very low-quality evidence and it suggests no effect of this therapy [30].

- *Mesenchymal stem cell-based therapy*. Some data suggest, in a mouse model of sepsis, the use of mesenchymal stem cells to restore mitochondrial function in satellite cells [26].

Experts involved in ICU-AW agree about the need for large randomized controlled trials with strict application of diagnostic criteria to evaluate these strategies [1,30,63,65–67].

CONCLUSION

ICU-AW is a frequent complication of ICU stays and is associated with morbidity and mortality. Physical examination at admission, regularly repeated during the ICU stay, is the cornerstone of diagnosis. Electrophysiological methods contribute to characterization into critical illness polyneuropathy, critical illness myopathy and critical illness neuromyopathy. The management of ICU-AW is essentially preventive: minimizing sedation and immobilization, limiting the use of drugs associated with ICU-AW. Insulin therapy for blood glucose control (< 110 mg/dl) and early mobilization could improve prognosis. No specific pharmacological intervention has been proven. Short-term complications include extubation failure and longer duration of MV, contributing to a longer ICU and hospital length of stay. Extubation of these patients can be a real challenge and may require tracheostomy to facilitate ventilator weaning. Moreover, the neurological deficit may persist after ICU discharge, being part of the post-ICU syndrome. It highlights the importance of following these patients by intensivists after ICU discharge.

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FIGURES

Figure 1. Different parts of the neuromuscular system can be involved during critical illness. Depending on the structure involved, ICU-acquired weakness can be divided in three subcategories: critical illness polyneuropathy (peripheral nerve), critical illness myopathy (muscle) and critical illness neuromuscular blockade (neuromuscular junction).
Abbreviation: ICU, intensive care unit.

Figure 2. Management of ICU-acquired weakness. This figure presents the steps of management when ICU-acquired weakness is suspected and its prognosis. Risk factors are separated according to whether they appear to be modifiable (box colored in green) or not (red).
Abbreviations: ICU, intensive care unit; ICU-AW, ICU-acquired weakness.

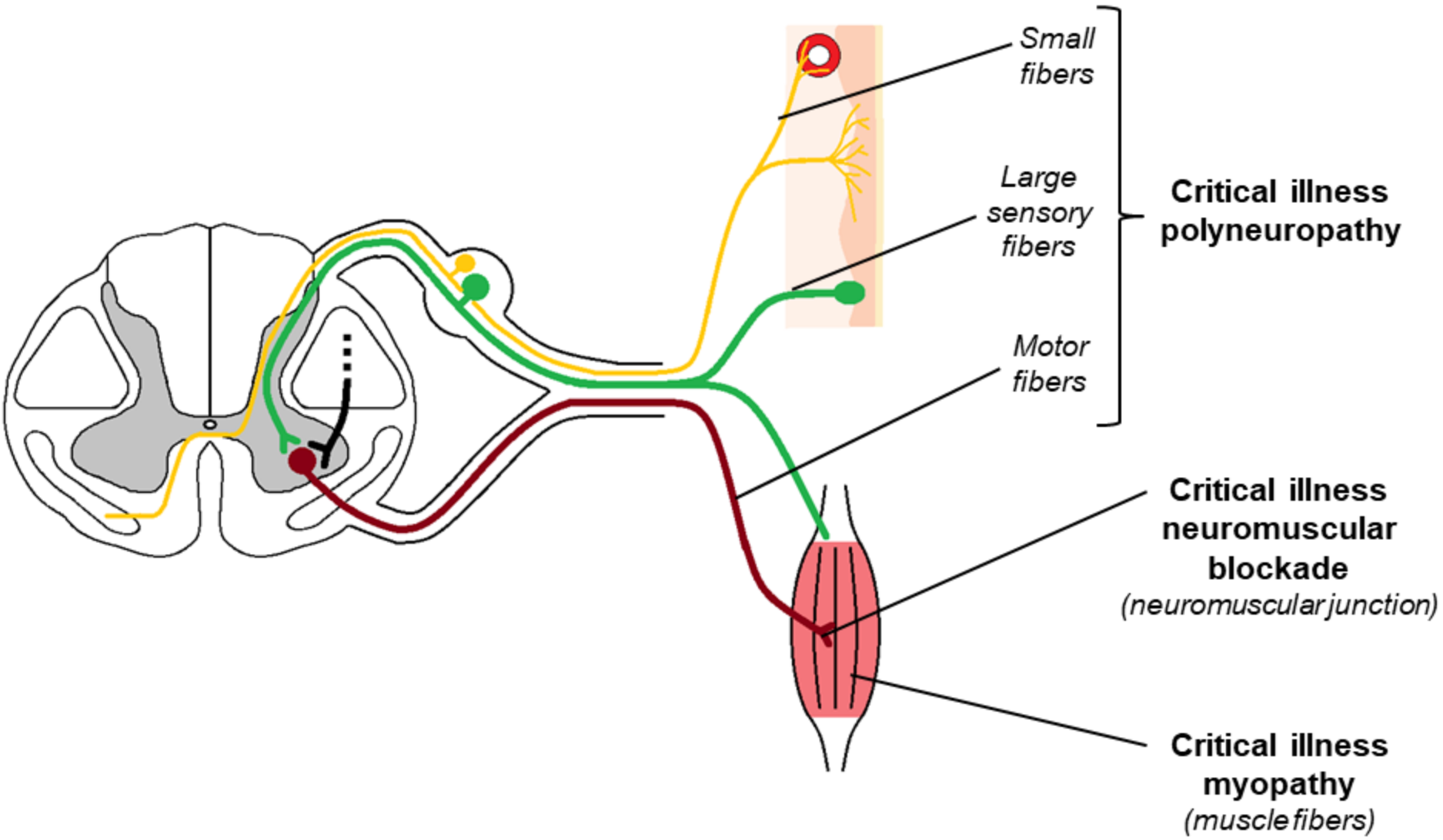
TABLES

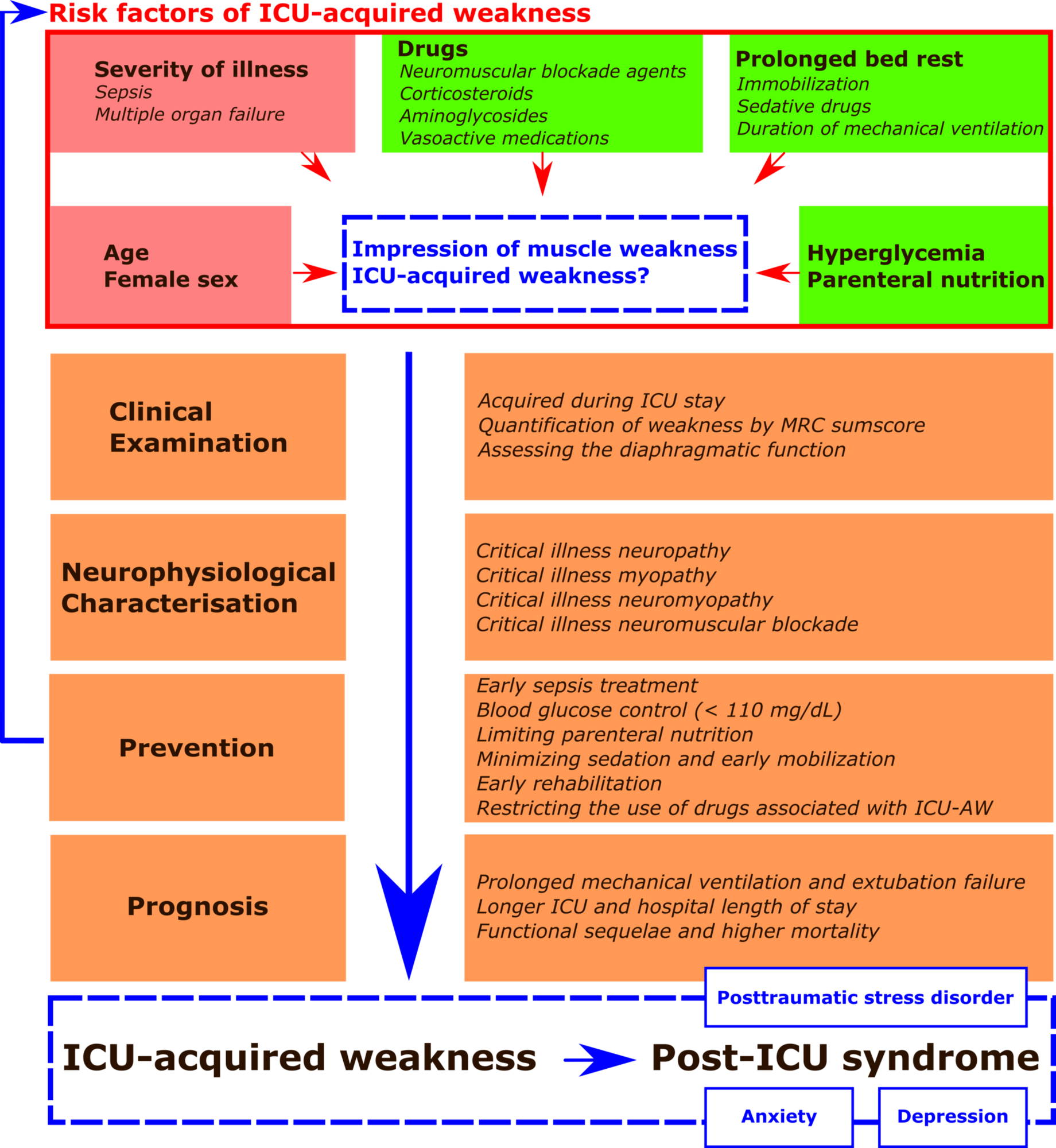
	Risk factors	**References**
Modifiable	Hyperglycemia	[29–31]
	Parenteral nutrition	[32]
	Drugs	
	Neuromuscular blockade agents	[32–34]
	Corticosteroids	[17,35,36]
	Vasoactive medications	[37]
	Aminoglycosides	[28]
	Sedation / Prolonged bed rest	[22,38]
	Duration of mechanical ventilation	[17,39]
Non-modifiable	Severity of illness; Sepsis and inflammation; Multiple organ failure	[17,37,40]
	Female sex	[17,39,41]
	Older age	[37,39]

Table 1: Main risk factors of intensive care unit-acquired weakness. Risk factors are separated according to whether they appear to be modifiable or not.

MRC score	
0	No visible contraction
1	Visible contraction without movement of the limb (not existent for hip flexion)
2	Movement of the limb but not against gravity
3	Movement against gravity over (almost) the full range
4	Movement against gravity and resistance
5	Normal
Muscle groups tested on both sides	
Abduction of the arm Flexion of the forearm Extension of the wrist Flexion of the leg Extension of the knee Dorsal flexion of the foot	

Table 2: Medical Research Council (MRC) scale: a useful and quick tool to quantify weakness in ICU-AW. The MRC-sumscore is a summation of the strength of 6 muscle groups tested on both sides according to the MRC scale. MRC-sumscore ranges from 0 (tetraplegia) to 60 (normal strength). Adapted from [45].
Abbreviation: ICU-AW, intensive care unit-acquired weakness.


Small fibers
Large sensory fibers
Motor fibers
Critical illness polyneuropathy
Critical illness neuromuscular blockade
(neuromuscular junction)
Critical illness myopathy
(muscle fibers)


Risk factors of ICU-acquired weakness
Severity of illness
Sepsis
Multiple organ failure
Drugs
Neuromuscular blockade agents
Corticosteroids
Aminoglycosides
Vasoactive medications
Prolonged bed rest
Immobilization
Sedative drugs
Duration of mechanical ventilation
Age
Female sex
Impression of muscle weakness
ICU-acquired weakness?
Hyperglycemia
Parenteral nutrition
Clinical Examination
Acquired during ICU stay
Quantification of weakness by MRC sumscore
Assessing the diaphragmatic function
Neurophysiological Characterisation
Critical illness neuropathy
Critical illness myopathy
Critical illness neuromyopathy
Critical illness neuromuscular blockade
Prevention
Early sepsis treatment
Blood glucose control (< 110 mg/dL)
Limiting parenteral nutrition
Minimizing sedation and early mobilization
Early rehabilitation
Restricting the use of drugs associated with ICU-AW
Prognosis
Prolonged mechanical ventilation and extubation failure
Longer ICU and hospital length of stay
Functional sequelae and higher mortality
ICU-acquired weakness
Post-ICU syndrome
Posttraumatic stress disorder
Anxiety
Depression