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Intensive Care Unit Acquired Weakness (ICU-AW): a brief and practical review

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Abstract

Intensive care unit-acquired weakness (ICU-AW) is an increasingly complication of survivors of critical illness. It should be suspected in the presence of a patient with a flaccid tetraparesis or tetraplegia with hyporeflexia or absent deep tendon reflexes and difficult to weaning from mechanical ventilation in the absence of different diagnoses. Important risk factors are age, sepsis, illness duration and severity, some drugs (neuromuscular blockers, steroids). Electrophysiological studies have shown an axonal damage of involved peripheral nerves (critical illness polyneuropathy). However, muscle can also be primitively affected (critical illness myopathy) leading to ICU-AW with inconstant myopathic damage patterns in electromyographic studies. Mixed forms can are present (critical illness polyneuromyopathy. Although the pathophysiology remains obscure, the hypothesis of an acquired channelopathy is substantial. Electroneuromyography is crucial for diagnosis. Muscular and nerve biopsies are necessary for diagnosis confirmation. Aggressive treatment of baseline disease, prevention, through avoiding or minimizing precipitating factors, strict glycemic control, and early rehabilitation combining mobilization with physiotherapy and muscle electrical muscle stimulation, are the keys to improving recovery of the affected individuals. This narrative review highlights the current literature regarding the etiology and diagnosis of ICU-AW.

Keywords

Intensive Care Unit Acquired Weakness (ICU-AW); Electrodiagnosis; Critical illness

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Introduction

Sir W. Osler did the first description of weakness in critical illness patients in the pre-antibiotic era [1], when he described a rapid loss of flesh in a person with prolonged sepsis and multiorgan failure. At the end of ‘70s and first ‘80s, physicians and neurologists pointed their attention in some patients that developed weakness of the limbs, arms or both with absent or hypoactive deep tendon reflexes, atrophy or loss of muscle fibers, fasciculations and frequently tetraparesis or tetraplegia after recovery from severe sepsis or other devastating inflammatory states [2-8]. These observations were more frequent as survival rates among patients in the intensive care unit (ICU) increased, and ICU-acquired weakness (ICU-AW) increased relevance for care providers outside the ICUs. Since then, numerous case series and observational studies of ICU-AW have led to an explosion in the number of terms used to describe this syndrome (critical illness polyneuropathy (CIP), critical illness myopathy (CIM), CRIMYNE, etc.) [9-11]. As a result, only recently a new scheme to diagnose and classify ICU-AW has been proposed to ensure consistent identification of ICU-AW patients [12]. Motor weakness may be related to (1) pre-existing neuromuscular disorder leading to ICU admission, (2) new-onset or previously undiagnosed neurological disorder, or (3) complications of non-neuromuscular critical illness. Neuromuscular syndromes related to ICU treatment consist of CIP, CIM, and prolonged neuromuscular blockade (PNB). They are recognized as a frequent cause of newly acquired weakness in ICU patients. Using this diagnostic definition, ICU-AW can be recognized more quickly permitting more uniform reporting of affected patients by intensivists.

By definition, ICU-AW is a tetraparesis or tetraplegia with hyporeflexia, or absent deep tendon reflexes muscle wasting, and difficulty weaning from the ventilator. Evaluation of these patients is based on neurological examination, detailed electrophysiological investigation, serum creatine kinase (CK) level, knowledge of clinical setting and predisposing factors, other laboratory studies as needed, and histological examination of muscle biopsy. Without electrophysiological studies, it is impossible to define and to characterize ICU-AW, phrenic nerve conduction, diaphragm electromyography, blink reflex, and the technique of direct muscle stimulation (DMS) could be employed together with conventional nerve conduction studies and needle electromyography. Today, ICU-AW should be suspected in any patient who develops generalized muscle weakness or impossibility to wean from the mechanical ventilator after recovering from a severe critical illness [4-8]. Primary differential diagnoses of critical illness related paralysis are incidental Guillain-Barré syndrome (GBS) and unmasked myasthenia gravis. Less frequent diagnosis to consider are atypical presentation of amyotrophic lateral sclerosis (ALS), polymyositis or other myopathies, and precipitation of porphyria or rhabdomyolysis due to drugs used in the ICU. Recently a poliomyelitis-like flaccid paralysis due to West Nile virus infection was reported [13]. A subgroup of patients with myasthenia gravis with muscle-specific tyrosine kinase antibody is noted to present as respiratory crisis [14]. Although no specific treatment exists for ICU-AW, understanding its etiology, pathophysiology, and risk factors may be significant for the prevention. Because the diagnosis and the management of ICU-AW can be sometimes difficult, this narrative review aims to help in organizing a practical approach to the diagnosis and management of ICU-AW patients.

Incidence

The real incidence of ICU-AW is unclear and varies between studies. This variability reflects different populations, risk factors, definitions of this syndrome, absence of diagnostic criteria widely validated and the difficulty to differentiate all clinical forms adequately [6-9]. It ranges between 7% in patients undergoing liver transplantation [15] to 33% in patients admitted to the intensive care unit with status asthmaticus [16]. Recent reviews report an incidence of 30 to 46%, mainly, secondary to sepsis and multi-organ dysfunction syndrome (MODS) [10,17]. The incidence is also higher (30-60%) in patients with acute respiratory distress syndrome (ARDS), especially in patients with long-term (> 1 week) duration of mechanical ventilation [7,18,19]. Seventy percent of patients with sepsis may suffer from CIP [6]. In children, the risk is less well defined as there are no prospective clinical and electrophysiologic studies.

Short- and long-term outcomes

ICU-AW appears to influence short and long-term measures of outcome. However, the risk of selection bias in published studies is high due to the combination of varied definitions of neuromuscular impairment and the use of selected cohorts. When the combination of severe sepsis, septic shock, and coma are present, mortality is near to 100% [7,8,20,21]. However, there is not yet a definite cause-and-effect relationship. No conclusive evidence exists to refute the possibility that poor outcomes and weakness may only reflect the type and severity of the patient's underlying pathology [22]. Furthermore, muscle wasting and weakness are common among ICU-AW survivors in long-term follow-up studies [23]. Latronico and colleagues evaluated 36 studies (n=263 patients) reporting long-term outcomes in heterogeneous ICU-AW populations [24], indicating a complete functional recovery (defined as breathing spontaneously and walking independently) in 68% of cases. A severe disability (defined as quadriparesis, quadriplegia, or paraplegia) was present in 28% of cases. Persisting milder disabilities (reduced or absent deep tendon reflexes, stocking and glove sensory loss, muscle atrophy, painful hyperesthesia, and foot drop) are common even in patients with complete functional recovery [25].

Risk factors

Table I summarizes the known clinical risk factors of ICU-AW. Multiple risk factors have been identified.

Risk factors	References
Advancing age	Bercker et al. [18], De Letter et al. [20]
Female gender	De Jonghe et al. [26]
Increased severity of illness	de Letter et al. [20], De Jonghe et al. [26], Bednarik et al. [27]
Systemic inflammatory response syndrome	Jaber et al. [28], Levine et al. [29]
Multiorgan system failure	De Jonghe et al. [26]
Sepsis	Garnacho-Montero et al. [30]
Hyperglycemia	Van den Berghe et al. [31]
Medications	Latronico et al. [8], Bercker et al. [18], de Letter et al. [20], De Jonghe et al. [26], Bednarik et al. [27], Garnacho-Montero et al. [30]
Corticosteriods	De Jonghe et al. [26]
Neuromuscular blocking agents	MacFarlane and Rosenthal [31], Leatherman et al. [32]
Aminoglycosides	Latronico et al. [8], Bercker et al. [18] de Letter et al. [20], De Jonghe et al. [26], Garnacho-Montero et al. [30]
Parenteral nutrition	Waldhausen et al. [33], Marino et al. [34]
Long duration of mechanical ventilation	De Jonghe et al. [26]
Catabolic state	Garnacho-Montero et al. [30], Trojaborg et al. [35]
Immobility	Levine et al. [36]
Combination of any of the above factors	Hund et al. [37]

Table I. Intensive Care Unit Acquired Weakness (ICU-AW) risk factors

Undoubtedly, important risk factors are age, sepsis, the duration and the severity of illness, as measured by ICU admission Acute Physiology and Chronic Health Evaluation score or Sequential Organ Failure Assessment score, systemic inflammatory response syndrome (SIRS), and MODS [18-22]. The use of neuromuscular blocking agents, vasopressors, corticosteroids, aminoglycosides and opioids, principally fentanyl, were also associated to ICU-AW. Only anecdotal reports link ICU-AW and administration of parenteral nutrition with the speculation that the use of intravenous fat emulsions with high amounts of polyunsaturated fatty acids could cause axonopathy [33,34]. Furthermore, additional risk factors include neurological compromise, hyperglycemia, hypoalbuminemia, hyperosmolarity, parenteral nutrition, renal failure with or without replacement therapy, female sex, joint contractures, and muscle wasting from catabolism and physical inactivity also contribute to ICU-AW [8,10,17,38,39]. Short-term immobility impairs microvascular function and induces insulin resistance [40], increases production of pro-inflammatory cytokines and reactive oxygen species, resulting in muscle proteolysis and a net loss of muscle protein and subsequent muscle weakness [41]. Prolonged immobility leads to decreased muscle protein synthesis, increased muscle catabolism, and decreased muscle mass, especially in the lower extremities. However, the presence of so many risk factors suggests that several factors act synergistically in the development of ICU-AW.

Clinical Picture: evaluation and diagnostic criteria for ICU-AW

The classical clinical findings are flaccid tetraparesis, frequently symmetrical with hypo or areflexia (major finding); atrophy and loss of muscle mass (minor finding) [4-8,25]. An initial examination should be performed upon admission to the ICU, with subsequent examinations paired with daily awakenings or when patients show signs of clinical improvement, allowing cooperation with a more comprehensive examination. The diagnosis of ICU-AW should begin with routine physical and neurological examination of a patient that is weak following an episode of critical illness with the use of the Medical Research Council (MRC) scale. The MRC score is a tool that help to graduate the muscle strength of various muscle groups in the upper and lower extremities [36]. It ranges from 0 to 5, with higher scores indicating greater muscle strength [36]. It has maximal punctuation of 60. A combined score of 48 points is a cut-off for presumptive diagnosis of ICU-AW [26]. Patients with ICU-AW according to the MRC score should undergo serial evaluations, and if persistent deficits are noted, electrophysiological studies, muscle biopsy, or both are warranted. Unfortunately, the MRC scale has several limitations due to discrimination and a potential ceiling effect, and we need better bedside tools for identifying the presence of ICU-AW.

Furthermore, weakness can also have a broad differential diagnosis. Table II summarizes common diseases that cause weakness in ICU patients.

Onset of ICU-AW may not be easily appreciated. It is often brought to the attention because of flaccidity and wasting of extremities or difficulty in weaning the patient from mechanical ventilation. Standard neurological examination should be adapted to patient clinical condition because patients' cooperation is often difficult to obtain, muscle strength testing may be inadequate and sensory examination not reliable. Acute motor deficits due to central nervous system (CNS), upper motor neuron injury may cause hypotonia and hyporeflexia similar to lower motorneuron lesions, and clinical differentiation between central and peripheral causes becomes difficult. Neuromuscular and CNS involvement may also be coincidental. Three major features usually point toward CNS involvement: asymmetric neurologic signs (hemispheric lesion), altered mental status (diffuse encephalopathy), and cranial nerve palsies (brain stem lesion). Appropriate imaging (computed tomography, magnetic resonance imaging) and electroencephalogram usually provide the diagnosis. Many spinal cord

Localization	Pre-existing	Previously undiagnosed/new-onset	Critical illness related
Spinal cord	Trauma	Acute ischemia	Not described
	Infarction	Epidural abscess	
	Transverse myelitis	Acute transverse myelitis	
Anterior horn cell	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis (predominant diaphragm weakness)	Hopkins syndrome
	Poliomyelitis (West Nile virus)	West Nile virus poliomyelitis	
Peripheral nerve	Guillain-Barre´ syndrome	Incidental Guillain-Barre´ syndrome	Critical illness polyneuropathy
	Chronic inflammatory demyelinating polyneuropathy	Porphyria, vasculitis, toxic, compressive	
Neuromuscular junction	Myasthenia gravis	Unmasked myasthenia gravis	Prolonged neuromuscular blockade
	Lambert-Eaton syndrome	Atypical myasthenia gravis (predominant respiratory weakness, muscle-specific tyrosine kinase antibody)	
	Botulism	Toxic	
Muscle	Muscular dystrophy	Rhabdomyolysis	Critical illness myopathy
	Polymyositis	Toxic myopathies	
	Periodic paralysis	Polymyositis	
	Metabolic/congenital	Myotonic dystrophy	
	Mitochondrial	Adult-onset acid maltase deficiency Pyomyositis Hypokalemic Hypophosphatemic	

Table II. Diseases and syndromes causing weakness in patients in the ICU: differential diagnosis

lesions, such as acute transverse myelitis, epidural abscess, and spinal cord infarct, may present as causes of ICU-AW. In the presence of flaccid weakness due to spinal shock, upper versus lower motor neuron paralysis cannot be distinguished. Presence of sensory level on trunk (when it is possible to investigate), Babinski sign, flexor spasms, loss of anal reflex, loss of sphincter control, and arms weaker than legs are some useful signs of spinal cord involvement. Magnetic resonance imaging of the spine is the most useful procedure in any suspicion of a spinal cord lesion. The main clinical features of neuromuscular diseases are weakness and wasting of extremities, hypotonia, and hyporeflexia/areflexia, with or without respiratory and/or cranial musculature involvement. The diseases of the anterior horn cell, neuromuscular junction, and muscle produce pure motor syndromes. Most peripheral nerve disorders have sensory and motor findings. Clinical distinction among these categories may be difficult in the ICU setting because of the impossibility in eliciting signs, overlapping features and simultaneous occurrence of more than one syndrome. Some helpful clinical signs are asymmetric weakness and fasciculations (ALS, viral poliomyelitis); paresthesia, sensory deficits, and distal symmetric weakness (peripheral neuropathy); cranial nerve palsies and dysautonomia (GBS); and combination of ptosis and weakness of eye closure (myasthenia gravis, prolonged neuromuscular junction blockade). Given the complexities of ICU-AW, a standard and practical definition is evidently difficult. To date the nosologic scheme by Stevens et al. [10,12] is a reasonable classification. ICU-AW should be applied in cases in which a patient is noted to have clinically detected weakness

	CIP	GBS
Prodromal conditions	Sepsis and multiple organ failure	Gastrointestinal or respiratory infection
Clinical presentation	Onset of the disorder usually after intensive care unit admission	Onset of the disorder usually before intensive care unit admission
	Often characterized by fairly symmetric limb muscle weakness sparing cranial nerves;	Infections precede the onset of progressive weakness and sensory disturbances
	Sensory deficits less prominent	Frequent cranial nerve involvement
Cerebrospinal fluid	Usually normal	Albumin-cytologic dissociation
Electrophysiology	Axonal motor and sensory polyneuropathy	Demyelinating polyneuropathy or unresponsive nerves, abundant spontaneous activity Axonal motor and sensory polyneuropathy
Nerve ultrasound	Elevated mean muscle echotexture and fasciculations in more arm and leg muscle groups with lower punctuations at the ultrasound pattern scores (UPS) at the examination of peripheral sensorimotor nerves (A), roots and vagus (B), and sural nerve (C)	Sonographic evidence of higher cross-sectional area values (CSA) of the ulnar, radial, tibial nerve and brachial plexus with higher punctuations at the ultrasound pattern scores at the examination of peripheral sensorimotor nerves (A), roots and vagus (B), and sural nerve (C)
Magnetic resonance imaging	No significant findings	Occasional enhancement of spinal nerve roots
Biopsy	Primarily axonal degeneration of distal peripheral nerves without inflammation	Primarily demyelinating process with inflammation, or motor/sensory axonal degeneration, or motor axonal degeneration only
Treatment	No specific therapy, usually anti-septic treatment	Plasmapheresis, intravenous immune globulin
Outcome	Recovery may be spontaneous and of variable timing; 50% of patients with full recovery	Usually > 75% complete recovery

Table III. Differentiation between critical illness polyneuropathy (CIP) and Guillain-Barré syndrome (GBS)

with no plausible cause other than critical illness. ICU-AW, with documented polyneuropathy, myopathy, or both, can be subclassified.

CIP refers to ICU-AW with electrophysiological evidence of an axonal polyneuropathy. CIM refers to ICU-acquired weakness with myopathy that is documented electrophysiologically or histologically. CINM refers to electrophysiological or histologic findings of both CIP and CIM [10,12]. Knowledge of clinical background in which the weakness evolves is an essential guide to differential diagnosis. CIP often follows sepsis [30], SIRS [28,29] and MODS [26]. CIM often occurs in the setting of treatment with intravenous corticosteroids [26] and non-depolarizing neuromuscular blocking agents [31,32], such as in patients with asthma, pneumonia, organ transplant, and renal failure [7,16,24,31,37]. The contribution of electrophysiological studies has been invaluable in identifying the different clinical forms [4-6,8,11,24,42]. However, there are some difficulties to define electromyography and nerve conduction studies as accurate [4-6,8,11,24]. They are difficult to perform in many critically ill patients. The patients must be awake and able to collaborate; patients in the ICU are often not able to contract their muscles voluntarily. Tissue edema can confound nerve conduction studies. Further investigation with biochemical studies and muscle biopsy are often necessary to arrive at a definitive diagnosis. Elevation of creatine kinase (CK) levels is associated with muscle necrosis but is not of diagnostic use on its own due to low sensitivity. Muscle biopsy in ICU paralysis syndromes may be helpful in arriving at an accurate diagnosis or to classify the type of CIM. Nerve biopsy is only rarely indicated. Clinical, electrophysiological, and histological features of ICU-AW are summarized in Table III.

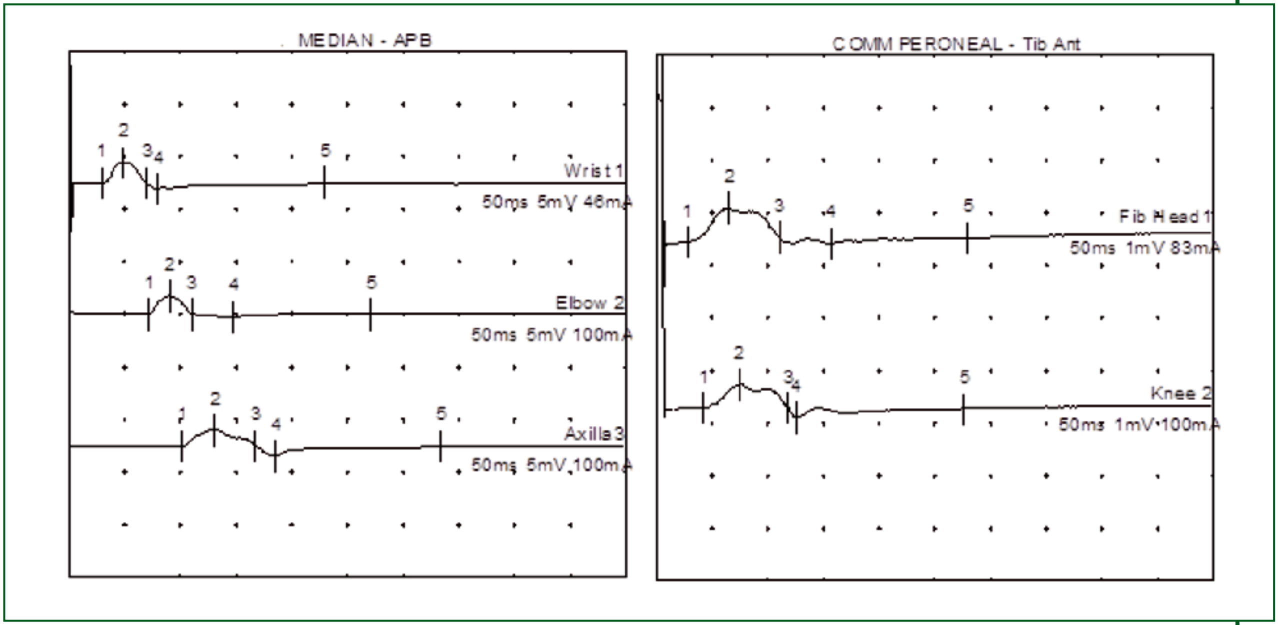

Figure 1. Typical nerve conduction studies in presence of CIP registered on median and common peroneal nerve and derived from abductor brevis pollicis (ABP) and anterior tibialis (Tib Ant), respectively. In CIP, CMAP amplitude is reduced (corresponding to loss of axons), with normal conduction velocity in surviving axons

Electromyography and nerve conduction studies

Electromyography is an essential method of making a final or differential diagnosis. A reduction in the amplitude of compound muscle action potentials (CMAP) or sensory nerve action potentials (SNAP), or both, with preserved conduction velocity and normal distal motor latencies, in addition to normal responses to repetitive nerve stimulation, may be seen within 2–5 days after the onset of symptoms. The reduction in amplitude often precedes clinical presentation and accompanying fibrillation potentials and positive sharp waves that may occur in the second or third week (Figure 1) [43]. The duration of CMAPs is an important indicator of CIM, and it accompanies the fall in amplitude [43]. CMAP duration can be 2-3 times longer compared to healthy controls and is most pronounced in lower limb nerves (Figure 2).

Electrophysiological screening is showing CMAP duration reductions below two standard deviations of the normal value accurately iden-

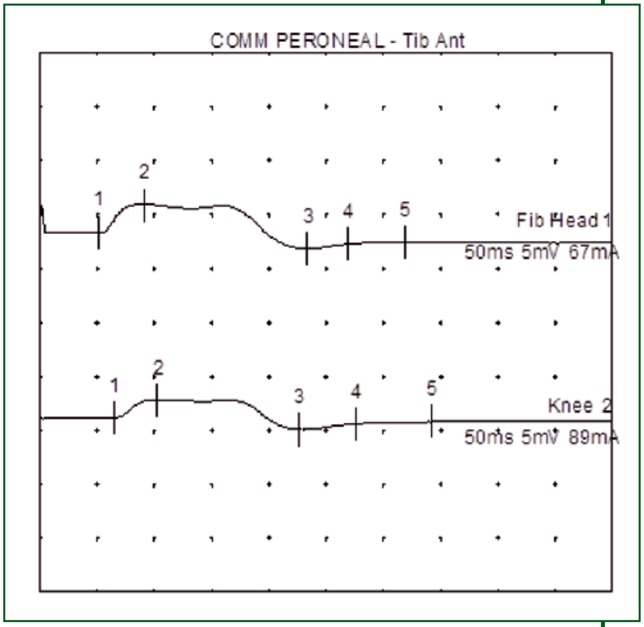

Figure 2. Typical nerve conduction study in presence of CIM registered on common peroneal nerve and derived from anterior tibialis (Tib Ant). In CIM, CMAP amplitude is reduced, together with an increase of CMAP duration with normal conduction velocity. Sarcolemmal inexcitability causes low amplitude CMAPs) that may have prolonged durations

tifies patients with CIP or CIM, increased duration of CMAP will permit to identify patients with CIM [44,45]. Patients admitted for sepsis or SIRS showing electromyographic signs of characteristic CMAP potentials in early stages, and an abnormal baseline nerve conduction study are more likely to develop acquired neuromuscular dysfunction with increased hospital mortality [44].

Baum et al. [45] identified four different clusters of electrophysiological impairment in patients with sepsis/SIRS, which enabled further differentiation of the severity of neuromuscular disturbances in sepsis-associated organ failure:

- Cluster 1: normal values for CMAP, SNAP, and nerve conduction velocity in all nerves, which accounted for 10% of total patients;
- Cluster 2: pathological values for CMAP in the lower extremities and other parameters normal, which accounted for 17% of patients;
- Cluster 3: moderate pathological values for CMAP, SNAP, and sensory nerve conduction velocity in upper and lower extremities and motor nerve conduction velocity in lower extremities, which accounted for 40% of patients;
- Cluster 4: severe disturbances of CMAP, SNAP, and nerve conduction velocity in upper and lower extremities, which accounted for 33% of patients.

Varying degrees of fibrillation potentials and positive sharp waves can be recorded in both CIP and CIM. Abnormal SNAPs are characteristic for CIP, although local edema may interfere with optimal sensory nerve stimulation and recording. CIM is characterized by significant slowing of the muscle fiber conduction velocity or even muscle fiber conduction block during the acute phase, which correlates with a prolonged CMAP duration and altered muscle fiber excitability [43]. The earliest electrophysiological sign of CIP is a reduction of CMAP amplitudes, with a minor change in latency. These changes are typical of axonal damage but are also associated with severe myopathy, including CIM. Fibrillation potentials and positive sharp waves may not appear in the muscle until 3 weeks after onset. Motor unit potentials (MUP), if they can be voluntarily activated by the patient, will often appear polyphasic and normal or somewhat low in amplitude, suggesting an associated primary involvement of muscle. These electrophysiologic changes, however, are not specific and are also produced by a primary myopathy. Despite electrodiagnostic technical difficulty in critically ill patients, it is important to demonstrate a reduction of SNAP amplitudes before a firm electrophysiologic diagnosis of polyneuropathy can be made; this finding is not present in many instances. There is some evidence that some patients with CIM demonstrate increased CMAP duration [46], but this finding needed further validation. In support of that, in vitro single muscle fiber excitability studies have demonstrated a reduction in muscle fiber conduction velocity that is inversely proportional to the degree of muscle weakness in CIM [47]. The CMAP amplitude prolongation was also proportional to the degree of weakness and phase of illness.

A simplified screening method of ICU-AW is based on the daily measurement of peroneal CMAP amplitude [48]. In a prospective multicenter study of 92 intensive care unit patients, a reduced CMAP amplitude on peroneal nerve by more than 2 standard deviations predicts neuromuscular complications of critical illness within a 67% specificity [48]. All affected patients developed the electrophysiological change within 13 days of intensive care unit admission with a median time of 6 days. This change in CMAP amplitude was abrupt over 1 day in most cases but took place over several days in others.

Repetitive nerve stimulation studies to demonstrate a defect in neuromuscular transmission should also be performed in suspicious cases. This defect does not occur in sepsis but will be present if neuromuscular blocking agents have been used. Their effects may persist beyond several hours for a number of days if the patient is in renal failure or liver failure [45]. Phrenic nerve conduction studies and, in some cases, needle electromyography of chest wall muscles and the diaphragm are safe and can establish respiratory muscle involvement in patients who are difficult to wean from the ventilator [50]. Electrophysiological features of CIM include reduction of CMAP amplitudes (less than 80%) and perhaps in some cases increased duration in 2 or more nerves with normal or near normal sensory nerve action potential amplitudes (more than 80%). There should be an absence of decrement on repetitive nerve stimulation. Myopathic changes should be seen on needle examination, with or without fibrillation potentials [51].

Tzanis et al. [52] have proposed that maximum inspiratory pressure may serve as a surrogate indicator for the assessment of CIP and CIM. The authors measured maximum inspiratory pressure using the unidirectional valve method, independent of the patient's ability to cooperate. A significant correlation was found between maximum inspiratory pressure and the MRC scale score ($r = 0.68$, $P < 0.001$) [52]. The findings indicated that maximum inspiratory pressure, estimated using the unidirectional valve method, may be useful for early detection of intensive care unit-acquired weakness [52]. Electrophysiological findings should always be correlated with clinical findings. In difficult cases, muscle biopsy may be required for a definite diagnosis.

Direct muscle stimulation (DMS)

To overcome the challenges of patient cooperation and completely avoid muscle biopsy, the method of DMS has been evaluated. First proposed by Rich et al. in 1996 [53], DMS was intended to differentiate between CIM and CIP. Both conditions demonstrate reduced nerve-evoked CMAP amplitude. Yet denervated muscle (as in CIP) should retain electrical excitability and after DMS, CMAP amplitude should be normal. CIM patients should exhibit loss of electrical excitability and both nerve- and after DMS, CMAPs should be diminished. The ratio of nerve stimulated CMAP to muscle stimulated CMAP amplitude should be more than 0.5 in CIM (and in normal controls) and less than 0.5 in CIP. Trojaborg and colleagues [35] applied those techniques in addition to the motor unit number estimates and quantitative electromyography to classify 22 consecutive patients with critical illness related weakness as having primarily neurogenic or myopathic features. These authors found that electrophysiological abnormalities supported a myopathy in all cases.

Muscle and nerve ultrasounds

Muscle and nerve ultrasounds appear as a new tool that can help to establish and early diagnosis of this entity [54,55]. In CIM, a controlled and observational study in patients with sepsis showed muscular fasciculations more frequently and in greater numbers of regions affected principally in proximal and distal arms and legs, additionally, 75% of them had alterations in normal echotexture of examined muscles [55]. In the same manner, the use of ultrasound pattern sum score (UPSS) and its sub-scores can help in identify CIP [54]. These methods until now are under investigation and cannot replace electroneuromyography and nerve conduction studies or muscular biopsy although showing high sensitivity, specificity, and predictive positive values.

Muscle biopsy

Muscle biopsy is still considered the gold standard for confirming muscle involvement in the disease process despite its invasiveness. Critical illness myopathy is pathologically classified into five subtypes: (1) thick filament myopathy; (2) acute myopathy with scattered necrosis; (3) acute myopathy with diffuse necrosis; (4) disuse cachectic myopathy; and (5) rhabdomyolysis (Figure 3) **[8,38]**.

Although unusual, myopathy can progress to frank rhabdomyolysis. CIP presents as morphological signs of axonal degeneration in both type 1 and type 2 fibers, resulting in extensive denervation atrophy of muscles. During recovery, muscle biopsy may show grouped atrophy of muscle fibers. Furthermore, angular atrophy of isolated scattered muscle fibers has been observed as part of an acute denervation process [8,38]. However, clinical characteristics and examination results should be carefully evaluated for the correct diagnosis of CIP and CIM [8,38].

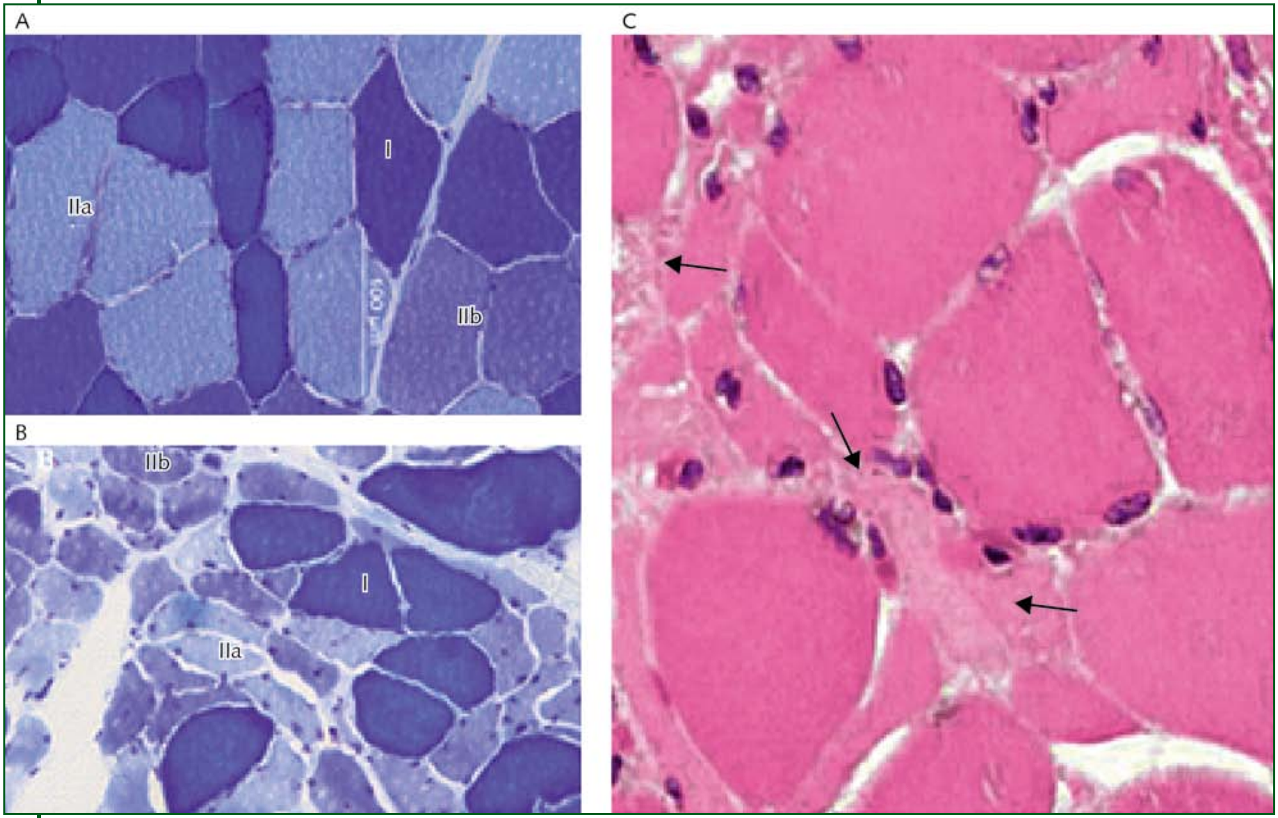

Figure 3. Muscle biopsy (vastus lateralis muscle) from a normal subject (A). ATPase/Toludine blue staining differentiates type I, IIa and IIb muscle fibres as indicated. (B) CIM. A predominant type II (fast twitch) muscle fibre atrophy. (C) Hematoxylin-eosin staining in CIM. Atrophic fibers stained poorly, and in some fibers, a feathery degeneration of the cytoplasmic content was seen (arrows)

ICU-AW clinical subtypes

Critical illness polyneuropathy (CIP)

CIP is a diffuse and symmetric sensorimotor axonal neuropathy [30]. In CIP we can observe a distal loss of sensitivity to pain, vibration, and temperature, and often the patients have difficult to breath spontaneously or to be weaned from mechanical ventilation due to phrenic nerve and diaphragm involvement [25,50]. The mechanism of axonal degeneration may be multifactorial, including: impaired oxygen and nutrient delivery from microcirculatory dysfunction in peripheral nerves, due to sepsis and/or hyperglycemia, and increased endoneuronal edema, due to cytokine-induced changes in microvascular permeability; and neuronal bioenergetics failure from mitochondrial dysfunction, due to increased uptake of glucose and subsequent reactive oxygen species generation [4,8,38]. Furthermore, cytokines may exert direct toxic effects on peripheral nerves, and there may be a humoral neurotoxic factor involved in the pathogenesis of CIP [4,8,38]. The morphologic features of CIP have been demonstrated through the biopsy of peripheral nerve and muscle [5]. There is a primary axonal degeneration of peripheral nerve motor and sensory fibers, but no evidence of inflammation, as may be seen in GBS. Muscle shows scattered atrophic fibers in acute denervation and grouped atrophy in chronic denervation. Immunohistochemistry of muscle biopsy specimens demonstrates upregulation of HLA-DR, the proinflammatory cytokine tumor necrosis factor-R75, and the anti-inflammatory cytokine IL-10 when compared to controls [56]. The only CNS manifestation is central chromatolysis of anterior horn cells and loss of dorsal root ganglion cells, secondary to the peripheral nerve axonal damage. No changes appear distinctive of CIP. A definite diagnosis of CIP requires that the following criteria be met: (1) The critically ill patient develops limb weakness or difficulty in weaning, after non-neuromuscular causes such as heart and lung diseases have been excluded; (2) electromyography shows axonal motor and sensory polyneuropathy; (3) absent decremental response to repetitive nerve stimulation [57].

Critical illness myopathy (CIM)

CIM occurs more frequently than CIP, and it is associated with a higher rate of recovery [58]. CIM represents a spectrum of ICU-acquired muscle pathology involving metabolic, inflammatory, and bioenergetics muscle derangements. CIM patients characteristically have early loss of muscle tissue (cachexy myopathy), but with conservation or slightly reduced deep tendon reflexes. In CIM, levels of CK are often high, and others blood exams can show evidence of SIRS, sepsis, and multiorgan compromise [7,24,38,59]. Frequently high levels of CK are observed [7,24,38,60]. Decreased oxygen and nutrient delivery to muscles, upregulation of protein catabolism by pro-inflammatory cytokines, decreased expression of myofibrillar repair genes, and an imbalance in anabolic and catabolic hormones contribute to CIM. The reported light-microscopic findings in specimens from CIM patients include muscle fiber atrophy (preferentially type II fibers), occasional fiber necrosis, regeneration, and decreased or absent reactivity in myofibrillar adenosine triphosphatase staining, corresponding to a selective loss of myosin filaments. This selective loss of myosin is practically pathognomonic for CIM [51,61]. To minimize the morbidity of an open muscle biopsy, some have proposed quantification of myosin/actin ratio by gel electrophoresis in core needle specimens (conchotome muscle biopsy technique) to diagnose CIM [62]. A definite diagnosis of CIM requires that the following criteria be met: (1) The critically ill patient develops limb weakness or difficulty weaning, after non-neuromuscular causes such as heart and lung diseases have been excluded; (2) compound muscle action potential amplitudes are less than 80% of the normal lower limit in two or more nerves without conduction block; (3) sensory nerve action potential amplitudes are greater than 80% of the normal lower limit; (4) needle electromyography shows short duration, low-amplitude motor unit potentials with early or normal full recruitment, with or without fibrillation potentials, in conscious and collaborative patients, or increased compound muscle action potential duration or reduced muscle membrane excitability by direct muscle stimulation in non-collaborative patients; (5) absent decremental response to repetitive nerve stimulation; (6) muscle histopathology shows primary myopathy [57].

Critical illness polyneuromyopathy (CINM)

CIP and CIM often coexist, commonly referred to collectively as CINM. Muscle that is functionally denervated (from CIP) and directly injured (from CIM) may have increased susceptibility to additional insults and injury (e.g., corticosteroid-induced myopathy). Furthermore, weakness from CINM may be enhanced by immobility [25]. When sought, myopathy is often present in conjunction with the established evidence for neuropathy [8,25]. For example, Latronico et al. demonstrated that 19 of 24 patients with CIP had evidence of myopathy when muscle biopsy was performed [25].

Prolonged neuromuscular blockade (PNB)

The condition may coexist with CIP or CIM and has been reported to progress to CIM on sequential studies. They are patients treated with high doses of nondepolarizing neuromuscular blocking agents such as vecuronium and pancuronium may have persistent weakness and fail weaning from the ventilator, even after the blocking drugs have been discontinued [43,49]. Examination shows generalized weakness, normal or reduced reflexes, and normal sensation. Bilateral ptosis and facial and jaw muscle

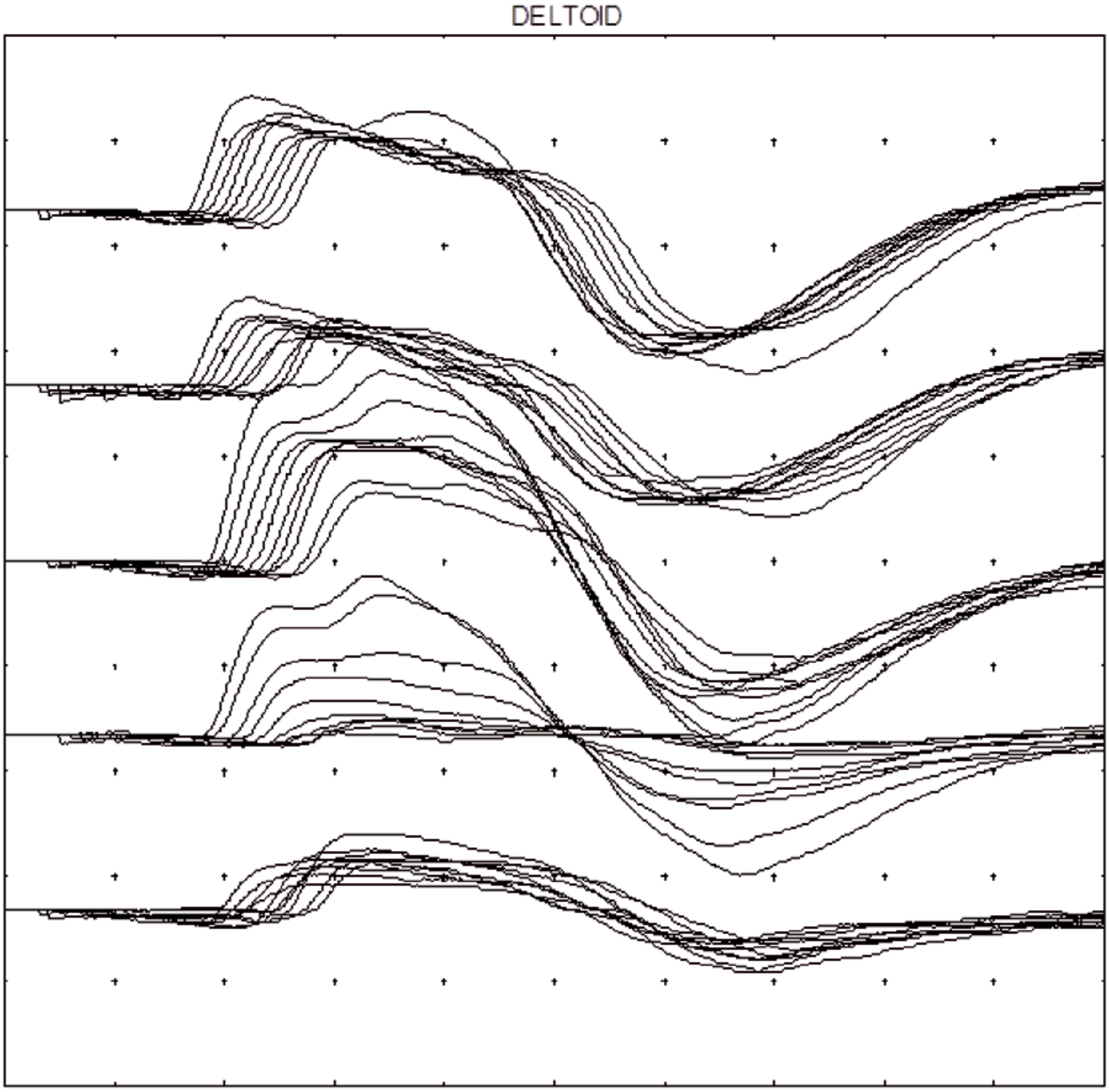

Figure 4. Repetitive nerve stimulation at a low stimulation rate (3-5 Hz) in a patient with prolonged neuromuscular junction blockade. Decrement response suggests neuromuscular transmission defect

weakness may be present [43]. Electrophysiologic features are reduced CMAP amplitude and decrementing the response on 2-3 Hz repetitive nerve stimulation (Figure 4). Patients with uncomplicated prolonged neuromuscular blockade recover completely, usually in 1-2 weeks.

Proposed diagnostic algorithm

To optimize the likelihood of patient interaction for neuromuscular assessments, we advocate the implementation of sedation protocols. Daily interruption of sedative infusions confers the opportunity for serial neuromuscular examination and reduces the duration of mechanical ventilation [63]. Careful implementation of the structured MRC examination should be employed and documented serially as

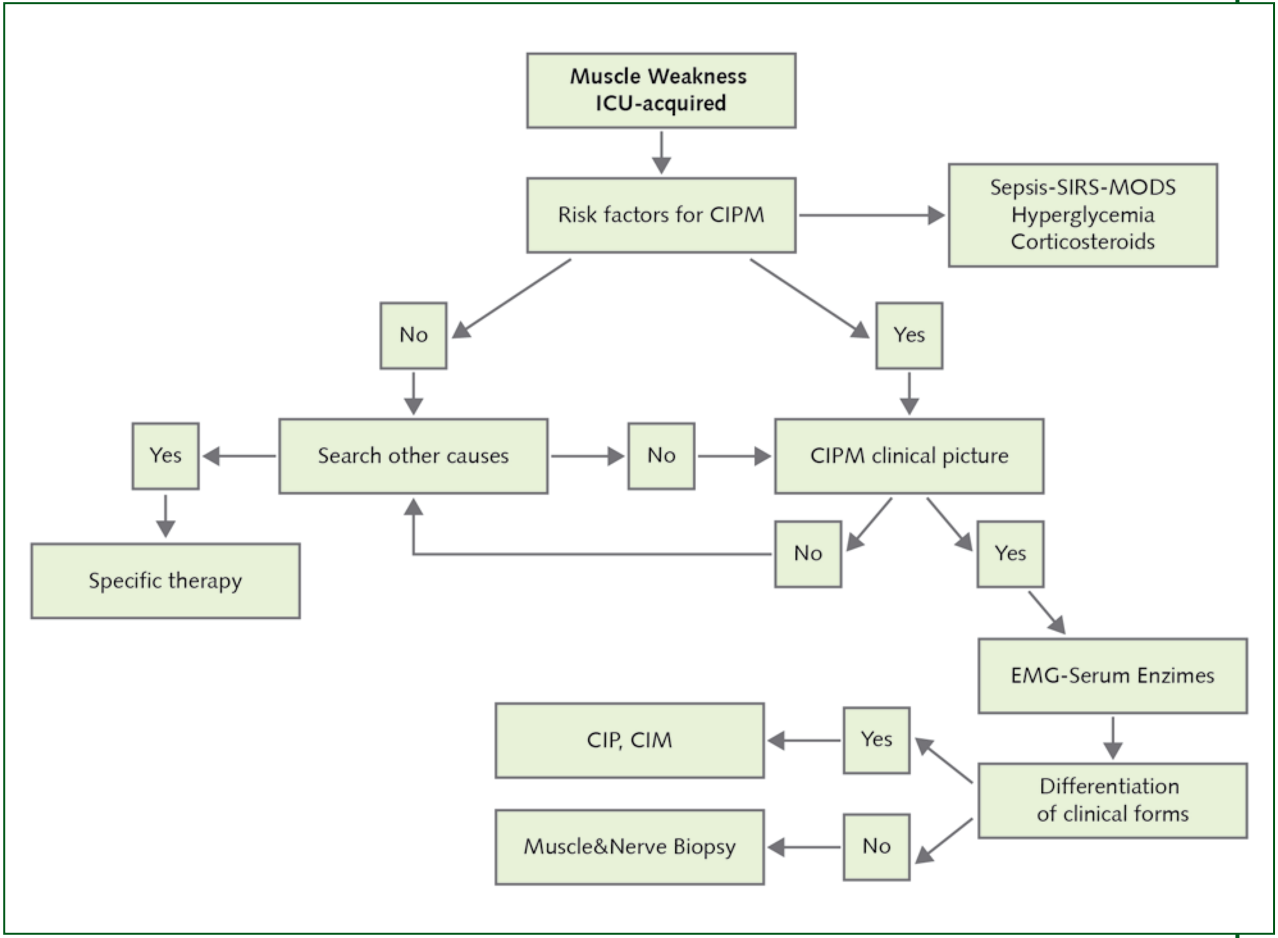

Figure 5. Practical algorithm for diagnosis of critical illness polyneuromyopathy

a matter of routine. Patients exhibiting fixed or focal motor defects or persistent altered sensorium despite adequate sedation washout should undergo more advanced diagnostics (i.e., CNS imaging, electrophysiologic studies, and/or muscle biopsy) (Figure 5).

The decision to perform electrophysiologic testing and/or muscle biopsy in routine care has created an ongoing debate in the medical literature about its utility. Advocates for routine clinical examination who reserve neurophysiological testing and biopsy for unusual or severe instances of weakness cite the limitations, costs, and risks of this testing is an useful and efficient strategy. Establishing a highly specific or physiologically based diagnosis does not translate to a specific pharmacologic therapy. Furthermore, therapies currently employed to limit ICU-AW should be applied to virtually all critically ill patients receiving mechanical ventilation.

Pathophysiological mechanisms

During the evolution of critical illness differents mechanisms of injury trigger and feedback to develop an adverse microenvironment for muscles and nerves. The muscular and nervous affectation does not escape the systemic involvement of different organs as a result of massive release of cytokines and other mediators that activate different cascade of mediators which produce electrical, metabolic, microvascular and bioenergetic disturbances (Figure 6) [8,28].

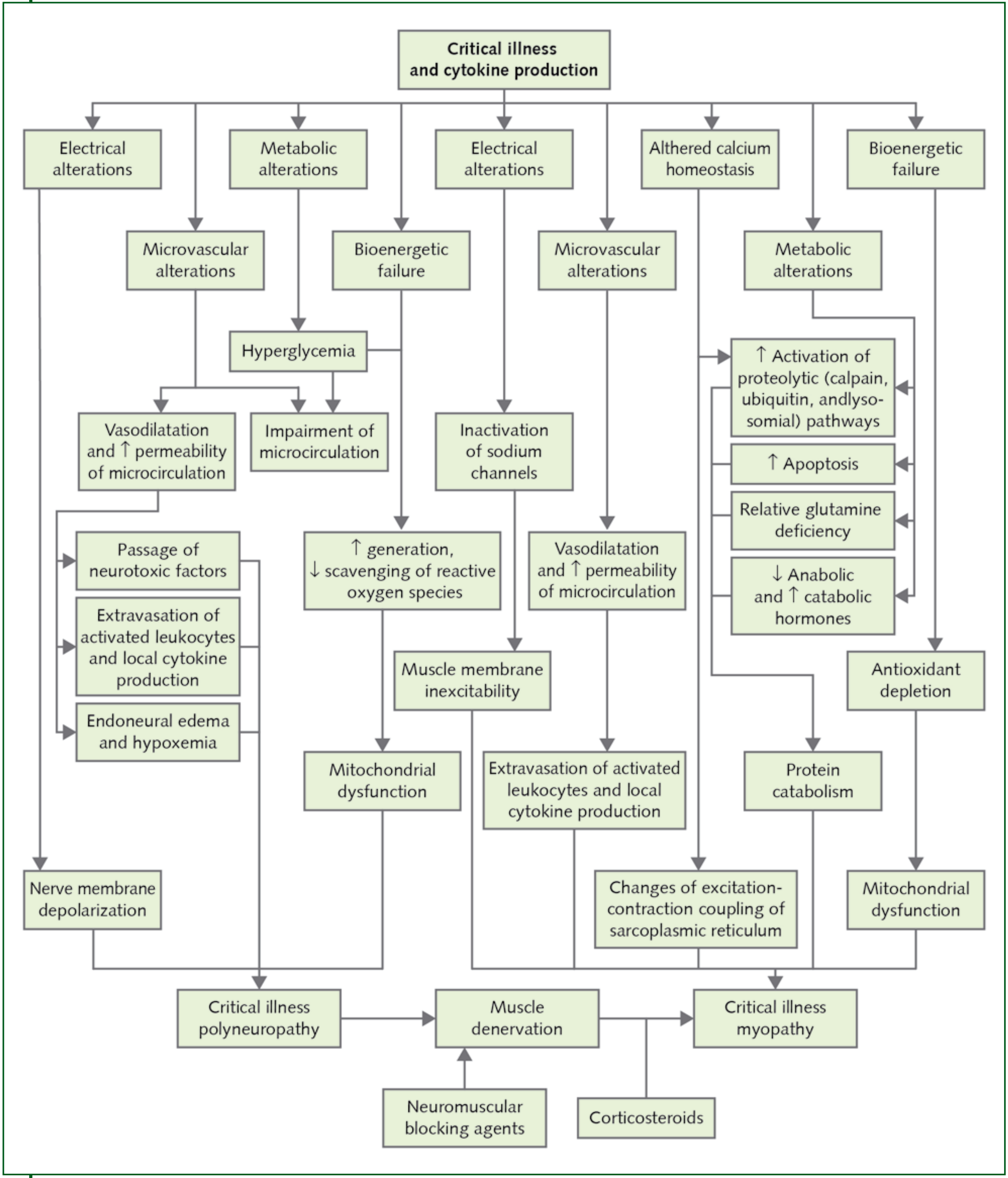

Figure 6. Pathophysiological mechanisms of ICU-AW

Inactivation of sodium ion channels

Rich and Pinter suggest that inactivation of sodium channels may contribute to critical illness related neuropathy, myopathy, or both [64]. During electrophysiological studies, severely affected muscle has been found to be electrically inexcitable to direct muscle stimulation [53]. In studies with animal models, this inexcitability has been proposed to be caused by changes (hyperpolarizing shift) in fast sodium channels leading to inexcitability of muscle fibers. In patients with septic shock, there are decreased QRS amplitudes and increased QRS duration; while, in patients who recovered from septic shock, the electrocardiographic findings return to normal [65]. These observations are consistent with the notion of an acquired channelopathy because of the strong association between severe sepsis and ICU-AW. This may result from post-translation modification of sodium channels by glycosylation or phosphorylation or from increased expression of the embryonic sodium channel isoform that causes a shift toward more negative potentials [64]. The inactivation of sodium channels provoke decrease or absence of nervous excitability, whereas in the muscles produce inactivity and decline of muscular strength. Biopsy specimens have demonstrated normal appearance of muscles and nerves or the presence of limited necrosis, suggesting that alterations in ICU-AW are primarily functional [8,24].

Metabolic changes

Hyperglycemia, hyperosmolality, and hypoalbuminemia enhance muscular and nerve microvascular permeability, developing edema, reduce antioxidant capacity and affect the microcirculation due to thrombosis, edema and vasoconstriction [6]. Disturbances of the microcirculation to nerve and muscle may also explain the effects of neuromuscular blocking agents, corticosteroids, and antibiotics, particularly aminoglycosides with their known neural toxicity. However, there has been no statistical proof that antibiotics cause peripheral nerve dysfunction in sepsis [66]. Through increased capillary permeability induced by sepsis, neuromuscular blocking agents could have a direct toxic effect on peripheral nerve axons. These neuromuscular blocking agents may also cause functional denervation through their prolonged neuromuscular blocking action. A combination of functional denervation due to neuromuscular blocking agents and the subsequent direct effects of steroids together with protracted immobility and a high-stress catabolic state in muscle might be a possible mechanism. CIP and the additional effects of neuromuscular blocking agents could denervate muscle, and steroids could then induce the typical myopathic changes. Both the rapidly evolving myopathy reported by al-Lozi and colleagues, which is characterized by destruction of thick filaments throughout the muscle fibers [67], and the acute necrotizing myopathy of intensive care may simply represent further stages of this process [68].

Microvascular changes

The pathophysiological mechanisms of ICU-AW are multifactorial and commonly invoked pathways include ischemia or injury via mediators of inflammation [61]. How systemic inflammation would produce nerve and muscle injury is unclear. In animal studies, inflammation of muscle tissue was found, represented by cellular infiltration and increased local levels of various inflammatory mediators. In human studies, high levels of various inflammatory mediators were found in muscle and nerve tissue of ICU-AW patients [61]. The expression of adhesion molecules on vascular endothelium suggests the possible contribution of increased vascular permeability. Expression of E-selectin, induced by sepsis is significantly elevated in the endoneurial and epineural vessels of patients with suspected CIP, supporting the idea that microvascular changes may contribute to the axonopathy of CIP [69]. A dysfunctional microcirculation leads to neuronal injury and axonal degeneration.This is believed to play a role in perpetuating local inflammation in peripheral nerves which suggests the endothelial-cell activation as described in models of sepsis, with microvascular leak and alterations in the microvascular environment. Moreover, cytokines that are secreted in sepsis have histamine-like properties that may also increase microvascular permeability [5]. Increased capillary permeability induces local tissue edema and activation of nitric oxide, causes arteriolar dilation, which may further slow capillary flow. Blood vessels supplying the peripheral nerves lack autoregulation, rendering these vessels susceptible to such disturbances. Tissue injury leads to the influx of inflammatory cells and the release of inflammatory cytokines. While these local phenomena may be important, measurement of more global markers of inflammation, such as interleukin-6 and tumor necrosis factor, has not shown them to be elevated in the serum of patients with CIP as compared to nonweak, critically ill control subjects [56]. Thus, essential nutrients fail to reach the organ parenchyma.

Bioenergetic disturbances

Severe energy deficits will result, inducing a primary axonal degeneration, most likely distally if highly energy-dependent systems involving axonal transport of structural proteins are involved. Bioenergetic failure is principally due to mitochondrial dysfunction with impaired capacity to generate ATP. Greater mitochondrial dysfunction has been observed in the skeletal muscle of patients who died from critical illness than in that of survivors of critical illness [44]. Hyperglycemia may also exacerbate this problem, perhaps by inducing neural mitochondrial dysfunction [61]. Failure of GLUT4 translocation from the perinuclear spaces to the sarcolemmal membrane was demonstrated to be a central mechanism of impaired glucose supply to muscle cells in CIM patients. There is a significant insulin resistance in critically ill patients as compared to healthy control subjects; insulin resistance is most severe in CIM patients. Electrical muscle stimulation corrected muscle-specific adenosine monophosphate-activated protein kinase failure, restored GLUT4 translocation in the sarcolemmal membrane, and prevented type-2 fiber atrophy in CIM patients [70].

Cellular apoptosis

Changes in calcium (Ca^{++}) homeostasis increases apoptosis and activation of proteolytic pathways. Different proteins degradative and apoptotic systems are found in muscle that have been implicated in CIM. Fiber atrophy is associated with myosin filament depolymerization that may be caused by increased expression of lysosomal enzymes and ubiquitin [71]. Patients who developed severe weakness after receiving high-dose steroids showed increased ubiquitin expression [72]. This suggests that the ubiquitin-ATP-dependent proteolytic system may be initiated by corticosteroid use. Serum amyloid A1 transiently accumulates within the first few days in muscle of critical illness myopathy patients and is in vitro induced by interleukin 6 and tumor necrosis factor-alpha [72]. Upregulation of part of the apoptotic system, specifically TGF-beta/MAPK, has been found to be uniquely involved in CIM [74]. There is also evidence linking proteolytic and apoptotic systems as mechanisms of muscle fiber atrophy, necrosis, and cell death. Caspase-3-mediated apoptosis has been shown to cause extensive cell death in multiple organ systems during sepsis [75]. Furthermore, hormonal changes include relative deficiency of glutamine, decrease of anabolic hormones and increase of catabolic hormones [76].

Protein degradation

Other mechanisms that contribute to muscle wasting during critical illness are derived from protein degradation exacerbated by profound hypercatabolism and prolonged immobility, particularly those with sepsis [30]. Muscle atrophy begins just after few hours of bed rest associated with deep sedation, a situation that applies to all muscle groups of the body, including the diaphragm. In the diaphragm, mechanical ventilation is associated with increased activity of the ubiquitin proteasome system, decreased levels of myosin heavy chain, and increased atrophic protein kinase B-forkhead box subgroup O (AKT-FOXO) signaling [29]. Muscle inactivity is a potent stimulus for protease activation leading to muscle protein breakdown and activation of the ubiquitin pathway of proteolysis. Immobility of the extremities, which is common in patients in the ICU, is related to the underlying illness in conjunction with prescribed bed rest and sedative-related immobility. Together with ubiquitin-proteasome system multiple proteolytic systems are also involved in muscle fiber atrophy, cathepsin B, lysosomal enzymes, and heat shock protein 72 [71].

Differential diagnoses

Differential diagnoses of ICU-AW commonly include GBS, metabolic neuropathies, toxic neuropathies, and neuropathies due to nutritional deficiencies. GBS, usually presents as symmetric, progressive, and ascending paralysis, sensory abnormalities, and areflexia, and 30% of patients require mechanical ventilation [77]. The nerve conduction velocity test shows decreased velocity in typical GBS, whereas normal conduction velocity and decreased action potential, both features of axonal neuropathy, can be seen in CIP and in axonal variants of GBS [77]. The major clinical difference between CIP and axonal variants of GBS is that GBS may follow an antecedent infective illness, surgery, or trauma for which the patient may have been initially admitted to the ICU [77]. Differentiation between BS and CIP is essential for the determination of therapeutic strategies, as intravenous immunoglobulin or plasma exchange is required in GBS [77], while supportive care is needed in critical illness polyneuropathy. Onset of clinical signs and electrophysiological changes in peripheral nerves and muscles during the development of CIP and myopathy can be rapid [18,28,38,78,79]. Albumin-cytologic dissociation in cerebrospinal fluid can help differentiate between the two diseases. The cerebrospinal fluid protein concentrations in patients with GBS are usually normal at the beginning of the disease, and increase in over 90% of patients by the end of the second week [77], whereas protein concentrations are usually unchanged in CIP and CIM. Furthermore, a nerve biopsy and detection of anti-ganglioside antibodies could be helpful in differentiating critical illness polyneuropathy from axonal GBS [77]. The criteria for differentiation are specified in Table IV.

Ionic abnormalities such as hypokalemia, hypophosphatemia, and hypermagnesemia, in addition to the use of several drugs including neuromuscular blocking agents, cancer chemotherapy, statins, and

Investigation	CIP	CIM	CINM
Physical examination	• Distal muscle weakness • Distal sensory deficit • Normal or depressed deep tendon reflexes	• Proximal muscle weakness • Normal sensory testing • Normal or depressed deep tendon reflexes	• Proximal and distal muscle weakness • Distal sensory deficit • Depressed deep tendon reflexes
Electrophysiology studies	• Decreased CMAP and decreased SNAP • Normal MUAP • Normal or near-normal • conduction velocity	• Decreased CMAP and normal SNAP • Decreased MUAP • EMG shows short duration, low-amplitude activity	• Decreased CMAP and SNAP • Decreased MUAP • EMG shows short duration, low-amplitude activity
Histology	• Axonal degeneration of distal • motor and sensory nerves	• Thick filament (myosin) loss, type II fiber (fast twitch) atrophy, necrosis	• Axonal degeneration and evidence of loss in myosin, type II fiber atrophy, and necrosis
Pathophysiological processes	• Nerve ischemia • Nerve microvascular injury Nerve mitochondrial injury • Sodium channelopathy	• Mitochondrial dysfunction • Oxidative stress • Sodium channelopathy • Ubiquitin–proteasome proteolysis	• Mixed

Table IV. Pathophysiological features of Intensive Care Unit-Acquired Weakness (ICU-AW).

CIM = critical illness myopathy; CINM = critical illness neuromyopathy; CIP = critical illness polyneuropathy; CMAP = compound muscle action potential; EMG = electromyography; MUAP = muscle unit action potential; SNAP= sensory nerve action potential.

antiretrovirals, should be differentiated because each can affect neuromuscular transmission and cause muscle weakness [80-82]. Propofol infusion syndrome, a syndrome involving severe metabolic acidosis, cardiac failure, rhabdomyolysis, renal failure, and hypertriglyceridemia after high-dose propofol (5 mg/kg/h) administration for long periods (> 48 hours), is also seen in intensive care units and should be taken into consideration [83]. Mild, chronic polyneuropathies such as diabetic polyneuropathy may affect predominantly the nerves of respiration. After admission to the critical care unit, sepsis may worsen a preexisting polyneuropathy. Occasionally, defects in neuromuscular transmission, myasthenia gravis, and Lambert-Eaton myasthenic syndrome present with primary respiratory failure. Diagnostic considerations in this group include anoxic myelopathy, affecting mainly anterior horn cells, which may result from cardiac arrest, atherosclerosis, surgery of the aorta or severe pulmonary disease [84].

CK levels vary in CIM but are usually normal or mildly elevated, except in acute necrotizing myopathy where CK levels are high. The signature pathological finding is a distinctive loss of thick myosin filaments. However, there can be various degrees of type 1 or type 2 muscle fiber atrophy as well as necrosis [71]. In an observational study of the first week of critical illness myopathy, Bierbrauer and colleagues described histological evidence in the vastus lateralis muscle of selective type 2 fiber atrophy coupled with depletion of myosin heavy chain IIa isoform messenger RNA in patients with inexcitable peroneal muscle membrane as defined by distal CMAP amplitudes below 3.0 mV [60]. There has been debate regarding the need for a muscle biopsy in patients with possible CIM [51,59]. The controversy surrounds whether the biopsy results alter treatment decisions. Although Lacomis and colleagues have listed histopathological findings of myosin loss as one of their diagnostic criteria, they do not advocate muscle biopsy in cases without apparent diagnostic uncertainty. Muscle ultrasound data from healthy controls were compared to that derived from septic patients in the first 2 weeks; most septic cases have elevated mean muscle echotexture and fasciculations in more arm and leg muscle groups [54,55].

There have been conflicting reports about the effect of critical illness neuromuscular complications on the intensive care unit mortality rate. A systematic literature review found no increase in adjusted mortality of intensive care unit patients with neuromuscular complications but demonstrated prolongation of mechanical ventilation and intensive care unit and hospital stay [10]. However, in a prospective cohort of severe sepsis cases who underwent weekly neurologic examinations and nerve conduction studies within 72 hours of developing severe sepsis, an abnormal baseline nerve conduction study was predictive of increased hospital mortality (55%), whereas none of the patients with normal baseline nerve conduction studies died [85]. Most of the affected patients had electrophysiological evidence of both critical illness myopathy and critical illness neuropathy.

Treatment and management

In the absence of specific therapy, the management involves the close collaboration of neurologists, neurophysiologists, and intensivists. The therapeutic strategies should be directed to the control of sepsis, SIRS and organ dysfunction and includes antibiotics to counteract infection, surgical drainage of an infected focus, and the use of inotropic drugs and fluid replacement to control hypotension. Several attempts at controlling early stage of the SIRS have shown variable results. These attempts include monoclonal and polyclonal antibodies directed against bacterial endotoxin, monoclonal antibodies to tumor necrosis factor-alpha, fusion protein constructs of soluble tumor necrosis factor receptors, IL-1 receptor antagonists [86], the platelet activating factor receptor antagonist, BN5202 [87], and the N-acetylcysteine [88]. There also was no beneficial effect of reducing disease severity using high intravenous immunoglobulins [89], and IgM-enriched intravenous immunoglobulin [90]. Avoiding or minimizing some pharmacological agents, such as corticosteroids and neuromuscular blocking agents represent the best strategy way for early recovering of muscle and nerve [3,4,8,25]. Both agents should be avoided or utilized at minor therapeutic dose and for shorter periods of time [3,4,8,25]. However, although the mean daily dose of corticosteroids may predict physical outcome at 1 year [91], a recent Cochrane review concluded there is no effect of corticosteroids on CIP, except for fewer new shock episodes [92]. Shortening the time in deep sedation is another useful strategy for preventing ICU-AW. Physical function at 1 and 2 years is negatively impacted by longer duration of ICU stay [93]. This strategy involves minimizing the sedation with the goal of getting patients up and out of bed. The discontinuation of deep sedation is a critical first step in optimizing patient activity and awareness. Deep sedation is associated with undesirable effects that can be avoided. It increases the possibility of hemodynamic instability, the incidence of delirium and prolongs the duration of mechanical ventilation with the associated risk of pneumonia ans sytemic infection that implies [7,8,21,94]. Moreover, profound sedation prolongs the time of immobilization and prevents adequate and effective rehabilitation favoring muscle atrophy [7,8,21,94]. Finally, over-sedation has economic consequences due to extension of stay in ICU and in the hospital. It is advisable as far as possible to implement protocols of daily interruption of sedation, in order to withdrawal as quickly as possible [94]. De Jonghe et al. noted that use of a sedation algorithm designed to allow patients to be more alert was associated with a 50% reduction in pressure sores, presumably because of reductions in sedative-related immobilization [95]. Furthermore, the interruption of daily sedative use during mechanical ventilation increases the percentage of days during which patients are awake and able to follow commands [63]. The changes in ICU care to reduce sedative use improve in-hospital activity levels in a group of patients in the medical ICU [96].

Currently, therapeutic interventions to prevent or attenuate ICU-acquired weakness and functional impairment after critical illness are limited to proper nutrition, moderate glucose control, early mobilization and rehabilitation [7,8,34,21]. To date, the role of nutritional and supplemental therapies include protein and amino acid supplementation, antioxidant therapy, and hormonal therapy [78]. However, studies examining nutritional supplementation are difficult to extrapolate to the treatment of ICU-AW, in that they typically focus on enhancement of the immune system or other global outcomes and not the correction of myopathy or neuropathy. Intake of specific substrates, such as glutamine and glutathione, might have a beneficial effect on recovering neuromuscular impairments in the critically ill patient. However, there are still no data to justify its use if the only purpose is to recover neuromuscular function, while aggressive renutrition schedules should be avoided in order to prevent re-nutrition syndrome and further deterioration of muscle function [78].

Insulin antagonizes the different routes of damage generated during hyperglycemia, and also has neuroprotective effects, so it is the agent of choice for blood glucose control strategies. Insulin exerts anti-inflammatory effects, endothelial protection, improvement of dyslipidemia, and neuroprotective effects in animals and is also an anabolic hormone [97]. Although intensive glucose control was earlier thought to be helpful in reducing the incidence and severity of critical illness polyneuropathy [31], the NICE-SUGAR Study argues against tight glucose control given the higher mortality risk associated with increased moderate to severe hypoglycemia [98]. Intensive insulin therapy should be avoided due to the risk of hypoglycemia [97,99,100]. The American Diabetes Association currently recommends target blood glucose of 144 to 180 mg per deciliter to reduce the risk of hypoglycemia in critically ill patients [101]. Therefore, according to a 2014 Cochrane update, intensive insulin therapy reduces ICU-AW (risk ratio 0.65), and it reduces the duration of mechanical ventilation, intensive care unit stay, and 180-day mortality. Because hypoglycemia is a risk, Cochrane reviewers recommend that consequences and prevention of hypoglycemia need further study [92].

The implementation of an early mobility and intensive rehabilitation program improves outcomes in ICU-AW patients [3,4,8,25]. When compared with a case series of patients with ICUAW who did not receive structured physical therapy, evidence suggested those who receive physical rehabilitation were more frequently discharged home rather than to a rehabilitative facility, although confidence intervals included no difference [57]. Passive mobilization prevents muscle atrophy, profound venous thrombosis and decubitus ulcers. Physical and occupational therapies increase the possibility to achieve good functional outcomes. Daily exercises especially targeted to the diaphragm and respiratory muscles help greatly in the process of weaning from mechanical ventilation. Other interventions show promise, but fewer data proving patient benefit exists. Furthermore, execution of a rehabilitation program requires a collaborative effort among members of the multi-disciplinary team to coordinate, care for, and provide safe mobilization of patients in intensive care units. Finally, electrical muscle stimulation (EMS) may be an alternative therapy for patients who cannot actively exercise or others disabling comorbidities and in patients unable to cooperate [102]. This technique may maintain muscle strength and joint range of motion, improve outcomes of ventilation, and reduce activity limitations [103].

Prognosis

ICU-AW is associated with increased mortality rate and rehabilitation problems [104]. Rehabilitation therapy is likely to be beneficial in speeding the recovery of these patients [105]. Prognosis for recovery from CIM is more favorable than that of CIP alone [17], unless muscle necrosis is severe, or CINM [106]. Children fair better than adults for a favorable recovery was thought to be as low as 50% [107]. However, if the polyneuropathy is severe, recovery may take months. In especially severe cases, recovery may not occur [6]. Neurophysiological studies performed at intervals can aid in determining prognosis of recovery [108].

Conclusions

ICU-AW is a frequent complication of critical illness. Recovery is often slow and incomplete in such patients, particularly those who are elderly. There are three principal clinical forms; CIP CIM, and the mixed form CINM. They are characterized by generalized muscle weakness including respiratory compromise that makes difficult to wean from mechanical ventilation. Electrophysiological studies can help in differential diagnosis. Occasionally, muscle biopsy is necessary. Aggressive treatment of risk factors is essential. Early diagnosis is important to apply all prevention measures that are needed. A multidisciplinary approach is essential and, due to the lacking of specific therapy, proper management is based on minimizing or avoiding triggers, controlling sepsis and inflammatory states, minimizing the use of sedation, strict glycemic control and early and aggressive plan of mobilization and rehabilitation to reduce muscle reconditioning and dysfunction.

Question for further research

There is some evidence that some patients with CIM demonstrate increased CMAP duration, but this finding needed further validation.

The review in brief	
Clinical question	Because the diagnosis and the management of ICU-AW can be sometimes difficult, this narrative review aims to help in organizing a practical approach to the diagnosis and management of ICU-AW patients.
Type of review	Narrative
Conclusions	Electrophysiological studies can help in differential diagnosis, occasionally, muscle biopsy is necessary. Aggressive treatment of risk factors is essential. Early diagnosis is important to apply all prevention measures that are needed. A multidisciplinary approach is essential, proper management is based on minimizing or avoiding triggers, controlling sepsis and inflammatory states, minimizing the use of sedation, strict glycemic control and early and aggressive plan of mobilization and rehabilitation to reduce muscle reconditioning and dysfunction.
Limitation	Lack of specific therapy.

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