

# Intensive care unit-related generalized neuromuscular weakness due to critical illness polyneuropathy/myopathy in critically ill patients

Efstratios Apostolakis · Nikolaos A. Papakonstantinou · Nikolaos G. Baikoussis · George Papadopoulos

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**Abstract** Thirty to fifty percent of critically ill patients admitted to the intensive care unit suffer from generalized neuromuscular weakness due to critical illness polyneuropathy, critical illness myopathy, or a combination of them, thus prolonging mechanical ventilation and their intensive care unit stay. A distinction between these syndromes and other neuromuscular abnormalities beginning either before or after ICU admission is necessary. These intensive care unit-related diseases are associated with both elevated mortality rates and increased morbidity rates. Generally, over 50 % of patients will completely recover. Most of them recover after 4–12 weeks, but some patients have been reported to keep on suffering from muscle weakness for at least 4 months. Prevention has a key role in the management of critical illness neuromuscular disorders, as no specific therapy has been suggested. Either prevention or aggressive treatment of sepsis can prevent critical

illness polyneuropathy and critical illness myopathy. The dose and duration of the administration of neuromuscular blocking drugs should be limited, and their concurrent administration with corticosteroids should be avoided. Intensive insulin therapy has also been proven to reduce their incidence. Finally, early mobilization via active exercise or electrical muscle stimulation plays a significant role in their prevention.

**Keywords** Critical illness · Paresis · Intensive care unit · Muscle weakness · Neuromuscular diseases · Rehabilitation

## Introduction

Over the last two decades, generalized neuromuscular weakness has constituted a severe, frequent, and persistent complication among critically ill patients admitted to the intensive care unit (ICU) due to infection, trauma, surgery, and burns [1–3]. Moreover, it is frequently responsible for prolonged mechanical ventilation [4] and prolonged ICU stay [5]. In 1977, MacFarlane and colleagues were the first to report critical illness-related severe weakness after neuromuscular blocking agents and corticosteroids administration in an asthmatic 24-year-old woman [6]. It was a little later, in 1984, when Bolton et al. [7] also observed severe polyneuropathy in five critically ill patients experiencing severe weakness and being dependent on mechanical ventilation. Newly acquired weakness in the ICU is mainly due to critical illness neuromuscular disorders including critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) [3]. The former is characterized by both motor and sensory fiber degeneration, primarily concerning lower limb nerves [1], whereas

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E. Apostolakis  
Cardiothoracic Surgery Department, University Hospital of Ioannina, School of Medicine, 45500 Ioannina, Greece

N. A. Papakonstantinou  
General Surgery Department, General Oncological Hospital “Agiou Anargyroi”, 41 Kaliftaki Street, 14564 Kifisia, Athens, Greece

N. A. Papakonstantinou (✉)  
12 Zilon Street, Rizoupoli, 11142 Athens, Greece  
e-mail: nikppk@yahoo.gr

N. G. Baikoussis  
Cardiac Surgery Department, L’Institut Mutualist Montsuris, 42 BD Jourdan, 75014 Paris Cedex 14, France

G. Papadopoulos  
Department of Anesthesiology, University Hospital of Ioannina, School of Medicine, 45500 Ioannina, Greece

the latter is characterized by fiber atrophy, fatty degeneration of muscle fibers, and fibrosis [8]. However, both of them lead to muscle weakness and paralysis in critically ill patients and they often coexist, making their differential diagnosis obscure [1]. Hereby, we will try to shed light on these dark clinical entities.

### Pathophysiology

Patients with systemic inflammatory response syndrome and multiple organ dysfunction experiencing respiratory insufficiency are prone to CIP/CIM [9–11]. Inflammation, apoptosis, thrombosis, and oxidant injury constitute the basis of both multiple organ failure (MOF) and peripheral neuromuscular abnormalities [2], so neuromuscular weakness because of CIP/CIM is due to neural system participation in MOF [5]. According to Bolton et al. [12, 13], microcirculation damage in peripheral nerves and muscles triggered by sepsis has a critical role in the CIP/CIM pathogenesis.

Pro-inflammatory cytokines such as TNF- $\alpha$  and IL1 induce a raise in the levels of E-selectin expression [1] in endothelium of epineurial and endoneurial vessels promoting endothelial cell leukocyte activation [14]. Activated leukocytes locally generate cytokines, damaging tissues [1]. Furthermore, sepsis-related cytokine secretion enhances microvascular permeability [13]. Consequently, the blood–nerve barrier becomes more permeable, allowing circulating toxins to directly impair the axons [12]. Some cytokines are also a direct neurotoxic factor for peripheral nerves [15]. Hyperglycemia and reactive oxygen species are additional adverse factors against the peripheral nerve microcirculation [16]. This microcirculation disturbance harms peripheral nerve [17] and organ perfusion [18] and results in significant energy deficits inducing primary distal axonal degeneration [19], which is the major pathological feature of CIP [2].

Metabolic, inflammatory, and bioenergetic changes compose the pathophysiology of CIM [16]. CIM is characterized by proteolysis aided by pro-inflammatory cytokines and increased apoptosis [20], elevated urinary nitrogen levels [2], and skeletal muscle hypercatabolism in combination with the general hypermetabolism of critical ill patients [21, 22]. Low protein/DNA levels and high extracellular water concentrations are additional findings of a muscle biopsy in critically ill patients [2]. Muscle membranes are often proved to be unexcitable by electrodiagnostic studies in CIM [16]. According to Rich et al. [23], the reasons why this happens are lower muscle resting potential because of denervation (from  $-85$  to  $-60$  mV), the lack of postdenervation down-regulation of membrane chloride conduction, and the shift in the voltage

dependence of sodium channel fast inactivation to more negative potentials ( $-11$  mV) [24, 25]. Moreover, altered nitric oxide generation in skeletal muscle as well as mitochondrial dysfunction impairs muscle membrane excitability in CIM [1, 16].

Administered corticosteroids and neuromuscular blocking drugs (NMBDs) may also have an impact on the pathogenesis of CIP and CIM [2, 10, 26]. NMBDs seem to either have direct toxic effects on the nerve or stimulate functional denervation of the muscle due to the enhanced microvascular permeability [13]. Finally, they may favor toxic effects of corticosteroids or inflammatory mediators [13, 16]. Furthermore, pathophysiologic changes of diaphragm also participate in the pathophysiology of CIP and CIM. Hence, if the diaphragm is inactive and mechanical ventilation is used for 18–69 h, noticeable atrophy of diaphragm myofibers occurs [27].

### Incidence

Overall, 30–50 % of critically ill patients suffer from CIP, CIM, or a combination of them [3]. Nevertheless, there are many factors strongly influencing the incidence of neuromuscular disorders, such as a patient's case-mix, diagnostic criteria, timing of diagnosis [1, 28], ICU stay length, and severity of sepsis [3]. Hence, 70 % of patients experiencing sepsis or systemic inflammatory response syndrome (SIRS) will suffer from CIP [12] and 60 % of patients suffering from acute respiratory distress syndrome (ARDS) will acquire either CIP or CIM [29]. Moreover, MOF is associated with a 100 % CIP prevalence [9], as well as critically ill patients in coma, all of whom will manifest CIP or CIM [8]. Mechanical ventilation duration of 4–7 days leads to CIP/CIM in 25–33 % of patients if they are clinically evaluated [10, 30, 31] and up to 58 % if they are electrophysiologically evaluated [32–34]. Finally, ICU stay of at least 7 days is related to a 49–77 % CIP/CIM prevalence [35–37].

### Diagnosis

#### Clinical evaluation of CIP/CIM

Female sex, age above than 50 years old, respiratory failure, SIRS, and ICU stay over 5 days are the typical characteristics of patients suffering from CIP/CIM [2]. CIP describes an acute axonal polyneuropathy in critically ill patients [1], whereas CIM refers to an acute, extensive, non-necrotizing myopathy in critically ill patients [1, 3]. Motor and sensory fiber degeneration primarily concerning lower limb nerves is the typical characteristic of CIP [1],

**Table 1** General features of critical illness polyneuropathy (modified from reference [40])

Critical illness polyneuropathy characteristics
Generalized or distal weakness
Flaccidity
Distal sensory deficits
Spared cranial nerves
Muscle atrophy with reduced or absent deep-tendon reflexes (possible reflexes recovery in one-third of patients)
Mechanical ventilation dependency with impaired respiratory mechanics
Usually normal CK levels
Normal cerebrospinal fluid
Reduced number of nerve axons without demyelination
EMG: reduction or absence of motor and sensory potentials without features of demyelination
Neurogenic atrophy in muscle biopsy; possible presence of critical illness myopathy characteristics
<i>CK</i> creatine kinase, <i>EMG</i> electromyography

**Table 2** General features of critical illness myopathy (modified from reference [40])

Critical illness myopathy characteristics
Generalized, mainly proximal, symmetric weakness
Flaccidity
Normal sensation
Usually spared cranial nerves
Muscle atrophy (possibly absent in early stages) with normal or reduced deep-tendon reflexes, possibly absent in severely affected muscles
Mechanical ventilation dependency with reduced vital capacity, tidal volume, negative inspiratory force
Elevated or normal CK levels
Normal cerebrospinal fluid
EMG: low motor amplitudes but normal sensory potentials, myopathic findings
Acute muscle fiber degeneration and thick filament loss without inflammation in muscle biopsy, abnormal myosin ATPase activity
<i>ATP</i> adenosine triphosphate, <i>CK</i> creatine kinase, <i>EMG</i> electromyography

whereas fiber atrophy, fatty degeneration of muscle fibers, and fibrosis are the main characteristics of CIM [8]. However, both lead to muscle weakness [1]. The main clinical features of CIP and CIM are flaccid and usually symmetrical weakness ranging from moderate paresis with reduced deep-tendon reflexes to severe quadriplegia with no deep-tendon reflexes, muscle wasting, and hypotonia with or without involvement of respiratory muscles and muscles innervated by cranial nerves [2, 3, 16]. Patients are often not capable of moving extremities in response to

pain, while their strong facial grimaces show they are awake [3]. Contrary to most myopathies, weakness equally affects distal muscles as it does proximal ones [38]. Legs are influenced more frequently than arms [7, 39]. Weakness in ICU patients may escape our attention until flaccidity and wasting of extremities or mechanical ventilation dependency [3] caused by diaphragmatic or intercostal muscles weakness [40] are observed. Sensory impairment, including a distal loss of sensitivity to pain, temperature and vibration, can also occur in patients with CIP [16]. Generally, SIRS and multiorgan dysfunction followed by generalized or distal weakness, distal sensory deficits, spared cranial nerves, and findings of axonopathy on EMG are basic clinical signs of CIP, whereas generalized or proximal weakness, elevated creatine kinase, and myopathic findings on EMG after the administration of high doses of NMBDs and corticosteroids are common clinical features of CIM [3] (see Tables 1, 2).

### Diagnosing CIP/CIM

Serum creatine kinase levels (CK), electromyography (EMG), nerve conduction studies, and muscle biopsy can help in the diagnosis of CIP/CIM [16]. Although CK level is often 10–100-fold increased in myopathy, making peak on the third or fourth day of the illness [3], it is usually normal in CIP and prolonged neuromuscular blockade [40], provided that muscle necrosis is absent or scattered [1]. After 10 days, the CK level is nearly normal even in CIM [3]. At least 15 % of patients present normal CK levels during their hospital stay [40]. Moreover, muscular traumas and needle EMG examination may cause CK levels to increase [3], as well as myoglobinuria and renal failure, which are associated with noticeable CK elevation [40]. Therefore, CK might not be a very useful parameter [16].

With regard to the electroneurographic pattern of CIP, the amplitude of the nerve action potentials (compound motor, sensory or both) is increased, whereas normal conduction velocity is maintained [1], only 3 days after onset of sepsis or ICU admission [30, 41]. On the contrary, reduced amplitude due to the reduced number of fibers and normal conduction velocity due to the normal myelin sheath of the rest of the fibers are typical of axonal neuropathy, whereas normal amplitude due to the normal number of fibers and reduced velocity due to demyelination characterize demyelinating neuropathy such as Guillain-Barré syndrome [1] (see Tables 1, 2).

These electroneurographic changes are prior to clinical signs as well as to denervation signs, such as fibrillation potentials and positive sharp waves, which may take place as late as during the second or third week of admission for critical illness [9, 42]. Nevertheless, these denervation

signs may also be present in myopathies [43]. CIP is also characterized by bilateral reduced or absent diaphragm compound motor action potential in about 50–80 % [44, 45] and almost normal phrenic motor latency [12, 46, 47]. On the other hand, normal compound motor action potential, normal F wave latency, and normal repetitive stimulation response are typical of CIM [48].

According to Latronico and Rasulo [49] and several other investigators [10], the Medical Research Council scale or handgrip dynamometry are useful to reliably indicate the limb muscle strength of the ICU patient. Regarding the Medical Research Council score, three muscular groups of both upper and lower limbs are evaluated from 0 to 5 with regard to muscle force forming a maximum sum score of 60 [10, 16]. A Medical Research Council sum score below 48 or mean Medical Research Council score below 4 (antigravity strength), and a force value less than 11 kg-force for men and less than 7 kg-force for women at dominant-hand dynamometry proves the presence of ICU-acquired weakness in ICU patients without previous story of neuromuscular abnormalities [49]. Nevertheless, this score does not shed light on the reason why weakness exists and its reliability is limited as the patients' wakeful status in order to cooperate is presupposed [16]. As far as respiratory muscle weakness is concerned, it can be diagnosed by evaluating the maximal inspiratory and expiratory pressures and vital capacity [49].

### CIP or CIM

Differentiation between CIP and CIM is often not possible, as they often coexist, and their clinical, electrophysiological, and histological features cover each other [1–3, 8, 16, 42]. Muscle biopsy, being the gold standard for the involvement of muscles [16], provides strong evidence for the diagnosis [2]. Severity of myopathic changes varies in CIM characterized by thick myosin filament loss, while CIP is associated with neurogenic atrophy (see Tables 1, 2). However, muscle biopsy use is limited because of its invasiveness and it is usually used provided other causes of myopathy like polymyositis are possible [3]. According to Bolton's study [13], muscle biopsy should be performed when clinical features suggest a myopathy. Stibler et al. [50] proposed that a percutaneous muscle biopsy obtained by a conchotome is a minimally invasive method that is useful for the rapid diagnosis of CIM in patients with decreased myosin-to-actin ratio.

Furthermore, direct muscle stimulation is an important diagnostic tool [2]. Conventional stimulation for example through the motor nerve will cause a reduced or absent action potential in patients with neuropathy. Direct muscle stimulation is related to a normal action potential in these

patients. On the contrary, as far as myopathy is concerned, both conventional stimulation and direct muscle stimulation are associated with reduced or absent action potential [1]. According to Lefaucheur et al. [51], reduced direct muscle stimulation amplitude and motor nerve stimulation to direct muscle stimulation amplitude ratio over 0.5 or prolonged direct muscle stimulation latency are typical of myopathy, whereas neuropathy is characterized by a motor nerve stimulation to direct muscle stimulation amplitude ratio of less than 0.5. Additionally, polyneuropathy is not possible when normal sensory nerve action potentials (SNAP) amplitude is recognized whereas SNAP are preserved in myopathy [52].

### Differential diagnosis

There are several disorders mimicking neuromuscular dysfunction related with critical illness which require a more specific therapy than CIP/CIM. These disorders can either pre-exist worsening during ICU stay or occur during ICU stay [2, 40]. Guillain-Barré syndrome, drug- and metabolism-induced neuropathies, myasthenia gravis [2], myopathy associated with hypokalemia, hypophosphatemia, or hypermagnesemia [40], uremia-related myopathy, and diabetes [2] constitute some of these disorders included in the differential diagnosis of CIP/CIM. Neuromuscular weakness can also be caused by acute myopathies because of rhabdomyolysis or acute polymyositis [3]. Brain stem infarct, hemorrhage, and central pontine myelinolysis leading to "locked-in" syndrome are additional causes of weakness included in the differential diagnosis of CIP/CIM. Acute transverse myelitis, epidural abscess, spinal cord infarct, traumatic spinal cord injury, and other spinal cord lesions causing generalized weakness should also be considered in the differential diagnosis [3].

### Risk factors

There is an abundance of risk factors related to CIP and CIM (see Table 3). Severity of illness and ICU-stay length are two of these [10, 30, 34]. Sepsis, SIRS, multi-organ dysfunction syndrome, multi-organ failure, female sex, severe asthma, ionic abnormalities, malnutrition, immobility [1, 53], duration of organ dysfunction [10], central neurologic failure, renal failure and renal replacement therapy, hyperosmolality, parenteral nutrition [26], low serum albumin [12], and vasopressor and catecholamine support [36] have all been recognized to make critically ill patients more prone to critical illness neuromuscular abnormalities.

Whether corticosteroids impair the critically ill patients' neuromuscular status is debatable [16]. The type and dose

**Table 3** Risk factors for critical illness neuromyopathy

Risk factors
Severity of illness [10, 30, 34] (sepsis, SIRS, multi-organ dysfunction syndrome, multi-organ failure [1, 53], duration of organ dysfunction [10])
Prolonged ICU-stay [10, 30, 34]
Prolonged neuromuscular blockade because of whichever possible cause [2]
Renal failure [2, 26, 54, 55]
Hyperglycemia [2, 10, 56]
Central neurologic failure [26]
Severe asthma [1, 53]
Malnutrition [1, 53], parenteral nutrition [26], low serum albumin [12]
Immobility [1, 53]
Female sex [1, 53]
Vasopressor and catecholamine support [36]
Abnormal serum lipid profiles [2, 57]
Ionic abnormalities [1, 53], hyperosmolality [26], metabolic acidosis [2]
Use of various antibiotics including aminoglycosides and clindamycin [2]

of corticosteroids themselves do not have any impact on the development of myopathy. On the other hand, neuromuscular blocking agents are an important risk factor for neuromuscular abnormalities development [2]. The majority of the neuromuscular blocking agents are metabolized by the liver and cleared by the kidneys. Hence, a long duration of neuromuscular blockade, lasting days or even weeks after discontinuation of drug administration, is possible to take place when large amounts of neuromuscular blocking drugs are administered to critically ill patients suffering from renal failure [6, 34]. Consequently, renal failure is a significant risk factor for prolonged neuromuscular blockade [2, 54, 55]. Hypermagnesemia, metabolic acidosis, and the concomitant use of various antibiotics including aminoglycosides and clindamycin also promote prolonged neuromuscular blockade but they are weaker risk factors than renal failure [2].

Hyperglycemia is also an important determinant of critical illness neuropathy and myopathy [2, 10, 56]. Finally, abnormal serum lipid profiles observed in critically ill patients also play a role in critical illness neuromyopathy, impairing normal function of some organs, including neural system [2, 57].

### Prevention/management

Prevention has a key role in the management of critical illness neuromuscular disorders, since no specific therapy

**Table 4** Preventing critical illness neuromyopathy

Prevention methods
Prevention or aggressive treatment of sepsis [2]
Early intravenous immunoglobulin administration in septic ICU patients [58] rehabilitation programs [60]
Managing mechanical ventilation dependency [61]
Careful patient positioning [16]
Limit the dose and duration of NMBDs administration [2]
Limit the duration of corticosteroids administration [2]
Avoid concurrent administration of corticosteroids and NMBDs [40]
Strict glycemic control via insulin therapy [16, 36, 37, 56, 75]
Early mobilization [76–78]
Electrical muscle stimulation [83–85]

*ICU* intensive care unit, *NMBDs* neuromuscular blocking drugs

has been suggested yet (see Table 4) [40]. Either prevention or aggressive treatment of sepsis can prevent CIP/CIM [2]. According to Mohr et al. [58], early intravenous immunoglobulin (IVIg) administration in septic ICU patients may prevent CIP development. However, the IVIg efficacy is doubted by a previous study in three patients [59] demonstrating failure of IVIg to change the clinical course of critical illness polyneuropathy. Rehabilitation programs [60], managing mechanical ventilation dependency [61] and preventing neuropathies caused by pressure by careful patient positioning, also participate in the successful management of CIP/CIM [16]. Nutrition schemes and nutritional interventions [62], total parenteral nutrition [63], antioxidant therapy [64], and the use of testosterone derivatives [65] and growth hormone [66] have also been applied to prevent CIP/CIM showing though no benefit with regard to muscle function [16].

Deep sedation caused by benzodiazepines (midazolam), propofol, and analgesics (fentanyl, morphine) is necessary for most critically ill patients in order to be mechanically ventilated [40]. Prolonged neuromuscular blockade should be prevented, so it is helpful to limit the dose and duration of NMBD administration, particularly in high-risk patients suffering from renal or hepatic failure [2]. Therapy with corticosteroids and NMBDs for over than 24–48 h grows the risk of acute myopathy [67], so the duration of their administration should be as short as possible [2]. Frequent interruptions in the drug administration of NMBDs in order to be cleared or pharmacologic reversal of neuromuscular blockade with a cholinesterase inhibitor can be useful to reveal a patient's movement, which is necessary to assure the absence of prolonged neuromuscular blockade in the ICU [2]. Furthermore, the concurrent administration of corticosteroids and NMBDs should be avoided as much as possible [40]. However, the role of corticosteroids is

controversial. There are both adverse [10, 68, 69] and positive reports [36, 37] with regard to their effects on CIP/CIM. ICU patients experiencing septic shock, ARDS, and acute asthma gain benefit from corticosteroids [16]. The duration and severity of MOF, which is an important risk factor for CIP/CIM, can also be decreased by the administration of corticosteroids [70]. Nevertheless, corticosteroids are an independent risk factor for assisted ventilation prolongation [37]. Hough et al. [71], who showed no impact of moderate doses of methylprednisolone on ICU-acquired neuromyopathy incidence, suggested that although corticosteroids result in more serious adverse events of neuromyopathy, they do not increase the total number of overall cases with ICU-acquired neuromuscular disorders.

Strict glycemic control (glucose levels between 80 and 110 mg/dl) via insulin therapy in order to avoid hyperglycemia also seems to prevent CIP/CIM [16], as insulin presents anti-inflammatory effects [72], protects the endothelium [73], improves lipid metabolism, and is also an anabolic hormone [16]. The mechanical ventilation duration and the patients' dependency on mechanical ventilation over 2 weeks are also reduced by intensive insulin therapy [36, 74]. According to van den Berghe et al. [56], tight glycemic control with insulin administration in critically ill patients reduced the percentage of neuromyopathy from 51.9 to 28.7 %. Moreover, intensive insulin therapy in patients staying in the ICU for at least 1 week reduced the prevalence of CIP/CIM from 49 to 25 % in the surgical ICU (SICU) ( $p < 0.0001$ ) and from 51 to 39 % in the medical ICU (MICU) ( $p = 0.02$ ) [36, 37, 56, 75]. Additionally, patients requiring mechanical ventilation for at least 2 weeks were decreased from 42 to 32 % in the SICU ( $p = 0.04$ ) and from 47 to 35 % in the MICU ( $p = 0.01$ ) [36, 37, 56, 75]. Remarkably, a recent study suggested that even corticosteroids have a protective role against neuro-myopathy when intensive insulin therapy is applied [37].

Recently, conventional methods of deep sedation and immobility in mechanically ventilated patients are doubted, as they gain profit from their early mobilization, which is also feasible and safe [76–78]. The European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients suggest that critically ill patients should be mobilized early [79]. Critical ill patients, who are early mobilized, get out of bed faster, stay less time in the hospital [80], are more often functionally independent after hospital discharge, are more likely to go home directly after hospitalization, and achieve better maximal walking distances while in the hospital as well as more ventilator-free days [81]. Rare adverse events are noticed after early mobilization [77, 80, 81]. Females, less sick patients (lower APACHE II score), patients who do not receive sedation and who are treated in

the respiratory ICU are more likely to ambulate early [82]. On the other hand, deep sedation, respiratory and hemodynamic instability, brain injury, severe delirium or dementia, terminal diagnosis, spine or limb injury, CPR on admission and preexisting severe physical handicaps are criteria that suggest a patient's exclusion from early mobilization [76]. Therefore, Hanekom et al. [78] recommended that a mobilization plan, depending on the patient's tolerance for exercise and safety, should be programmed for each patient admitted to an ICU in order to achieve the patient's early mobilization.

Electrical muscle stimulation (EMS), which is an alternative to active exercise [83], was reported to have a positive impact on muscle mass and strength preservation in critically ill patients [83–85]. EMS does not depend on patient cooperation, so it can be easily applied immediately after ICU admission [83, 85]. Catabolic effects of critical illness and immobilization to the muscle are reversed by the anabolic stimulus triggered by EMS [83–85]. EMS activates anti-inflammatory effects, improves microcirculation and mitochondrial function, promotes glucose oxidation, and the release antioxidant enzymes [83, 85]. Recent studies reported that not only does EMS lead to preserved muscle strength of directly stimulated muscle groups but it also results in muscle strength preservation of muscle groups not directly stimulated [83, 84]. Muscle mass of the stimulated muscle groups is also maintained [85]. Routsis et al. [83] suggested that 55-min EMS sessions per day in critically ill patients prevent CIP/CIM development and result in earlier weaning from mechanical ventilation and shorter ICU stay, thus decreasing morbidity. Therefore, EMS application is directly related to earlier rehabilitation and prevention of ICU-acquired weakness, as it promotes early mobilization, improves aerobic capacity, and shortens ICU and hospital stay [84].

## Prognosis

Elevated mortality rates are reported in ICU patients experiencing CIP/CIM [5, 26, 33, 34], so diagnosis of electrophysiologic abnormalities at an early stage has prognostic value [32, 34]. The mortality rate in patients with CIP is as high as 60 % and is associated with underlying diseases rather than with CIP/CIM itself [3, 86]. However, such high mortality may be due to the underlying critical illness [30]. Apart from high mortality rates, CIP and CIM are associated with high morbidity rates due to increased ICU and hospital stays [26, 33] and due to prolonged rehabilitation and mechanical ventilation dependency [16]. Muscle weakness and paralysis are caused, thus affecting rehabilitation [34] in up to 100 % of patients staying in the ICU for over 4 weeks [53]. Moreover,

assisted ventilation is required for 2–7 times more time in patients with critical illness neuromuscular disorders [12, 26, 31, 33], as the impairment of phrenic nerve and diaphragm is possible [12].

Over 50 % of patients completely recovered [12, 68, 87]. Most of them recovered after 4–12 weeks, but some patients have been reported to keep on suffering from weakness for at least 4 months [40]. Chronic disability is possible as clinical and neurophysiological signs may last for up to 5 years after ICU discharge [53, 88, 89]. Weeks are sufficient for clinical improvement in mild cases, while severe cases require months in order to improve in terms of physical disabilities [16]. In mild and moderate cases, rapid and full recovery, without any motor deficits or muscle weakness, is reported [12, 34, 53, 62, 68, 90, 91], whereas severe cases are related to incomplete recovery and high mortality [12, 62]. Tetraparesis, tetraplegia, or paraplegia is observed in up to 32 % of the most severely affected patients [68]. Even fully functionally recovered patients often suffer from persistent milder disabilities [16, 92]. According to Zifko et al. [91], six of 19 patients with CIP died in the first year, while 11 patients presented persistent neurological abnormalities impairing quality of life during 17 months after ICU discharge. In de Seze's study [68], 11 of 19 patients with severe CIP fully recovered, whereas eight patients died or suffered from persistent weakness 2 years after hospital discharge. Prolonged duration of fever, prolonged ICU stay, and weight loss were associated with a poor recovery [68].

## Conclusions

Critically ill ICU patients' clinical course is often complicated by CIP and CIM [1]. Weaning is delayed, rehabilitation is impaired, hospital and ICU stay are prolonged, and mortality is increased because of CIP and CIM [16]. A distinction between these syndromes and other neuromuscular abnormalities beginning either before or after ICU admission is necessary [3]. Therapeutic measures aim at the prevention of CIP/CIM via preventing or facing the most important risk factors. Either prevention or aggressive treatment of sepsis can prevent CIP/CIM [2]. Limiting the dose and duration of NMBD administration is helpful in preventing prolonged neuromuscular blockade [2]. Shortening the duration of corticosteroid and NMBD administration limits the hazard of acute myopathy [2]. Furthermore, although the role of corticosteroids is controversial, the concurrent administration of corticosteroids and NMBDs should be avoided, unless the latter are necessary [40]. In addition, intensive insulin therapy reduces the incidence of CIP/CIM as well as the duration of ventilator support dependency [16, 74]. Finally, early

mobilization, being absolutely feasible and safe, is beneficial for the patient's rehabilitation [76–78]. Recent studies report that EMS, which is independent from patient's cooperation, contributes in early mobilization and prevents ICU-acquired weakness [83–85].

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