Critical illness myopathy and neuropathy
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Purpose of review
To present the major pathophysiological and diagnostic features of critical illness myopathy (CIM) and polyneuropathy (CIP), and to discuss problems concerning the risk factors for CIM and CIP.

Recent findings
The pathophysiology of critical illness myopathy and critical illness polyneuropathy is complex, involving metabolic, inflammatory, and bioenergetic alterations. This review cites new evidence supporting several pathogenetic mechanisms. These include microvascular changes in peripheral nerves (with increased endothelial expression of E-selectin), the possible role for an altered lipid serum profile in promoting organ dysfunction (including nerve dysfunction), the damage or inhibition of complex I of the respiratory chain as a cause of muscle ATP depletion and bioenergetic failure, and the activation of specific intracellular proteolytic systems causing myofilament loss and apoptosis in CIM. The diagnostic role of direct muscle stimulation and the rapid quantification of myosin/actin ratio based on electrophoresis are also presented.

Summary
Basic and clinical research is unraveling the pathophysiological mechanisms of critical illness myopathy and polyneuropathy, and methods for rapid diagnosis are actively investigated. Future studies should better define the population at risk of developing CIM and CIP. In fact, although sepsis, multi-organ failure and steroids are often cited as risk factors, uncertainty remains due to the poor methodological quality of studies, or because of inferences that are exclusively based on animal studies. New simplified diagnostic techniques and machines for electrophysiological investigations of peripheral nerves and muscles in the intensive-care unit (ICU) patient would also be welcome.

Keywords
mitochondrial dysfunction, multi-organ failure, myopathy, neuropathy, polyneuropathy, sepsis

Introduction
‘Spontaneous weaknesses indicate disease.’ Hippocrates, 460–377 B.C.

The finding that critically ill patients may develop acute polyneuropathy that leads to muscle weakness and paralysis is fairly recent. The first systematic studies, conducted in the early 1980s, suggested critical illness polyneuropathy (CIP) was an uncommon syndrome [1], however clinical research in the last two decades has shown that CIP is an important, severe and persistent complication among critically ill patients admitted to the intensive care unit (ICU). Research has also demonstrated that CIP is often associated with critical illness myopathy (CIM). In fact, starting from the early 1990s, several studies based on muscle biopsies [2–15**, muscle–nerve biopsies [16] or specialized electrophysiological investigations [13,15**,17,18] have shown that CIM is as common as CIP. CIM and CIP often coexist, making their differential diagnosis difficult or even impossible. Many terms have been suggested to describe such an association, namely polyneuromyopathy [4,15**] critical illness myopathy and neuropathy (CRIMYNE) [16,19] and critical illness polyneuropathy and myopathy [12].

In this review, we present the major clinical, pathogenetic and diagnostic features of CIP and CIM, and discuss the recent research suggesting that metabolic, inflammatory, and bioenergetic alterations may play pivotal roles in causing peripheral nerve and muscle dysfunction in critically ill patients.

Critical illness polyneuropathy
CIP is an acute axonal sensory-motor polyneuropathy (Fig. 1), mainly affecting the lower limb nerves of critically ill patients.

Pathogenesis
Microcirculatory damage has long been postulated as a possible mechanism causing impaired peripheral nerve [20] and organ perfusion [21]. Bolton suggested a key role

Abbreviations
CIM critical illness myopathy
CIP critical illness polyneuropathy
DMS direct muscle stimulation
GBS Guillain–Barré syndrome
ICU intensive-care unit

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for excessive vasodilatation and aggregation of cellular elements through activation of adhesion molecules [20]. Recently, increased expression of E-selectin has been demonstrated in the endothelium of the epineurial and endoneurial vessels of peripheral nerves in critically ill septic patients with CIP [22]. E-selectin is not expressed on the vascular endothelium of small vessels under basal condition; its expression is considered a marker of endothelial cell activation. Increased expression of E-selectin, which is induced by proinflammatory cytokines such as TNF-α and IL1, may in turn promote endothelial-cell leukocyte adhesion and extravasation of activated leukocytes within the endoneurial space, where they can induce tissue injury with local cytokine production. Furthermore, cytokines increase vascular permeability, thus favoring the passage of neurotoxic factors into the endoneurium [20,23].

Although the evidence supporting a microvascular perturbation in sepsis and critical illness is robust, the direct involvement of intracellular mechanisms is also evident [24]. Sepsis and critical illness are complex conditions in which inflammatory and metabolic events at a vascular and cellular level contribute to organ failure. This is well demonstrated by the substantial reduction of mortality and morbidity (including CIP) in critically ill patients treated with intensive insulin treatment [25].

Combined vascular and cellular events may cause a nerve energy failure with reduced or absent nerve action potential, which in its early stages is a pure functional impairment that can be documented by electrophysiological investigations. With persisting critical illness, energy supply and use are not restored and histologic alterations ensue. Support for this theory comes from a previous study, in which we found altered nerve function with preserved nerve structure in patients undergoing early nerve biopsy, and altered function and structure in patients undergoing late biopsy [16]. Hotchkiss et al. [26] also showed a net divergence between in-vivo evidence of organ failure and absence of histologic evidence of substantial organ damage in patients dying of multi-organ failure, indicating that cellular energy crisis with consequent functional impairment can be a key process in critical illness.

**Diagnosing critical illness polyneuropathy**

The electroneurographic pattern in CIP is characterized by an amplitude reduction of the nerve action potentials (compound motor, sensory or both) with preserved normal conduction velocity (Fig. 1). Conversely, in Guillain–Barré syndrome (GBS), a demyelinating polyradiculoneuritis, amplitude is normal and velocity is reduced (Fig. 1). Even though such characteristic electroneurographic patterns are useful to distinguishing the two syndromes, it is the history and clinical findings that lead to the differential diagnosis.

CIP is a relatively common complication conceivably arising during the ICU stay in the most severe critically ill patients admitted to the ICU with a variety of medical,
surgical and traumatic causes. No studies have prospectively assessed the evolution of CIP starting at the time of ICU admission in patients CIP-free. GBS is a rare immune-mediated disease affecting 1–2 per 100000 previously healthy people. An infection, most frequently a Campylobacter jejuni infection with diarrhea, precedes by 2–3 weeks the onset of progressive weakness and sensory disturbances (tingling, numbness, sometimes pain) in two-thirds of cases. Importantly, inflammatory signs have subsided by the time neurologic signs become evident. In 30% of cases the progression of disease causes the involvement of the neuromuscular respiratory system with respiratory failure needing ICU admission and mechanical ventilation [27].

Clinical diagnosis is particularly important when dealing with GBS cases with axonal pattern (5% of cases) [28] or CIP cases with mixed axonal and demyelinating pattern [29]. Before CIP was characterized, GBS was often reported in critically ill patients after major surgery or trauma. These may well have been CIP cases [30], but this is still debated. Distinction between GBS and CIP is important not only from a nosological perspective but also for disease management, since specific treatments are available for GBS [31,32], but not for CIP.

How many patients develop critical illness polyneuropathy?

The real occurrence of CIP is enormously influenced by a patient’s case-mix, diagnostic criteria and timing of examination. Although reported percentages are rather impressive – 58% of patients with prolonged ICU stay [33], 70 to 80% of patients with sepsis, septic shock or multi-organ failure [34–37], 100% of patients with sepsis and coma [16] – the number of patients with CIP discharged from the ICU is small [19]. It is still unclear whether this is due to the fact that CIP complicates the clinical course of a subset of very severely critically ill patients or is due to selection bias. For instance, in one study conducted by De Jonghe et al. [38] inclusion criteria were mechanical ventilation lasting at least one week and recovery of consciousness. The study involved 5 French ICUs, lasted 15 months and enrolled 95 patients. Although the authors defined this population as unselected, several hundred patients had probably been admitted to their ICUs during the study period. This is common to all the series analyzed so far.

The method used to define diagnosis used can also influence the occurrence of CIP. Neurologic examination is less sensitive than electrophysiological evaluation, and would probably leave a substantial number of CIP patients undiagnosed. On the other hand, electrophysiological investigations would detect cases of CIP of little or no clinical relevance. Finally, the timing of examination is relevant, since CIP improves over time.

Critical illness myopathy

The term CIM describes an acute primary myopathy causing muscle weakness and paralysis in critically ill patients. In 1997, Leijten [39] proposed that CIM should be regarded as a correlate of CIP. In 1998, we [40] proposed CIM as a comprehensive term to describe those myopathies with pure functional impairment and normal histology (acute quadriplegic myopathy), as well as those with atrophy and necrosis. Necrosis can be subtle, requiring electron microscopy for diagnosis (thick filament myopathy), or it can be visible on optical microscopy, either as sparse, diffuse or even massive lesions (acute necrotizing myopathy). Recently, other authors have re-proposed this definition, indicating a list of major and supporting electrophysiological, histologic and biochemical criteria to diagnose CIM [41]. Apart from leaving out a formal definition of critical illness, which should be preliminary, some of the proposed criteria are questionable. For example, major EMG criteria require the patient’s collaboration, and cannot be used in unconscious patients; loss of myosin at histology can be lacking in pure functional forms; serum CK can be normal (as it commonly is) if muscle necrosis is absent or scattered; sensory nerve action potential can be abnormal since CIM and CIP may coexist. It is important to emphasize that CIM is a primary myopathy, that is, not secondary to muscle denervation. Histologic examination often reveals signs of both primary (necrosis) and secondary (type grouping following nerve regeneration) myopathy [16], indicating that CIM and CIP coexist.

Pathogenesis

In recent years, substantial progress has been made to explain how muscle may become unexcitable while maintaining a normal structure. Using an experimental model with denervated rat muscle fibers and high-dose steroid, Rich et al. demonstrated that the muscle may become completely unexcitable because of the combination of various events: denervation-induced reduction in muscle resting potential (from normal values of $-85$ mV to $-60$ mV), lack of postdenervation down-regulation of membrane chloride conduction [42], and shift in the voltage dependence of sodium channel fast inactivation to more negative potentials ($-11$ mV) [43,44]. The hyperpolarizing shift of voltage-dependence of sodium channel fast inactivation is of crucial importance to reduce excitability in both denervated and steroid-denervated fibers [44], and is mainly, although not exclusively, caused by steroids. Because a small percentage of denervated fibers also exhibit this same shift in fast inactivation, it appears that corticosteroid treatment simply increases the percentage of fibers that exhibit this change [44]. The density of embryonic sodium channel isoform is increased in the model of steroid-denervated fibers [42], however its level did not correlate closely with the shift in fast inactivation [45]. Rather, inactivation of both embryonic (Na$_1$,1.5) and adult (Na$_1$,1.4) sodium channels...
Mitochondrial dysfunction is another piece of the puzzle, which may be responsible for muscle function impairment. Brealey et al. showed that the severity of sepsis correlated with mitochondrial dysfunction, ATP depletion, intracellular glutathione depletion, and nitric oxide production in skeletal muscle [14]. The low activity of the complex I of the respiratory chain was probably caused by nitric oxide, a reactive oxygen and nitrogen species, and was facilitated by depletion of the intracellular antioxidant reduced glutathione. Damage or inhibition of complex I was in turn responsible for decreasing the mitochondrial capability to generate ATP. Bioenergetic failure is therefore an important pathogenetic mechanism underlying sepsis-induced muscle failure, similar to that described for peripheral nerve failure (see above). Whether bioenergetic failure correlates with muscle transmembrane resting potential and sodium channel alteration remains unanswered.

The ultimate effectors of proteolysis are intracellular proteolytic systems, namely the ubiquitin-proteasome, calpains, lysosomal and non-lysosomal systems [48–50]. Activation of proteolytic systems, particularly ubiquitin-proteasome and calpains, has long recognized to play a role in CIM [4,40,51]. Pro-inflammatory cytokines, together with decreased levels of anabolic hormones (insulin and insulin-like growth factor-1), and increased levels of catabolic hormones (cortisol, catecholamines and glucagon), generate a powerful catabolic effect, possibly to generate ATP. Bioenergetic failure is therefore an important pathogenetic mechanism underlying sepsis-induced muscle failure, similar to that described for peripheral nerve failure (see above). Whether bioenergetic failure correlates with muscle transmembrane resting potential and sodium channel alteration remains unanswered.

Diagnosing critical illness myopathy
Diagnosis of CIM and differential diagnosis between CIP and CIM are often not possible in ICU patients for several reasons. First, clinical differentiation is unreliable, because patients cannot cooperate for accurate sensory and (in some cases) motor testing. Second, needle electromyography can help distinguish between the two entities only with fully cooperative patients [39]. In the usual ICU condition, voluntary motor unit potential recruitment is often absent or nonsustained because of severe weakness or poor voluntary effort, therefore precluding a conclusive distinction between CIP and CIM based on recruitment patterns and motor unit morphology. Third, routine studies provide nonspecific data in both illnesses, including low-amplitude compound muscle action potential, fibrillation potentials and positive sharp waves. Preserved sensory nerve action potential amplitude is not a unique feature of CIM, since pure motor forms of CIP have been described [16,53]. Isolated sensory nerve action potential amplitude reduction rules out an ongoing myopathy, provided technical problems such as limb edema are excluded; however pure sensory CIP is exceedingly rare [53]. Finally, as previously cited, CIP and CIM often coexist.

Direct muscle stimulation (DMS) combined with standard investigation has been proposed to overcome some of these problems [17,18]. In DMS both the stimulating and the recording electrodes are placed in the muscle distal to the end-plate zone (Fig. 2) [54]. A patient with neuropathy will have a reduced or absent action potential when using conventional stimulation (i.e. through the motor nerve), but normal action potential when using DMS (Fig. 2b); in the case of myopathy, the action potential will be reduced or absent after both conventional stimulation and DMS (Fig. 2c). Despite the apparent simplicity of the technique, DMS is technically demanding and requires thorough practice to obtain reliable results [15**].

Muscle biopsy is an invasive method, and results are not immediately available. A percutaneous method using a conchotome reduces invasiveness to a minimum. Rapid methods (24 hours) to quantify the myosin/actin ratio based on electrophoresis are also being studied [55**]. Stiblet et al. showed that a mean value of the myosin/actin ratio was 1.37 (SD 0.21) in controls and 0.37 (SD 0.17) in CIM patients, without overlapping values [55**]. In cases of persisting muscle weakness or paralysis of uncertain cause, open muscle biopsy can rarely be indicated to exclude infectious causes; inflammatory infiltrates are typically absent in CIM.

How many patients develop critical illness myopathy?
The true occurrence of CIM is unknown. As for CIP, the patient’s case-mix, the diagnostic criteria used, and the timing of evaluation are factors influencing the occurrence of CIM. The crude proportion of critically ill patients reported to develop CIM varies substantially among centers and is useless, if population – the denominator of the proportion – is not clearly defined. As an example, the occurrence of CIM was 0.09% of patients admitted when all admissions in a 5-year period were considered (39 patients
Risk factors for critical illness myopathy and polyneuropathy

Sepsis, multi-organ dysfunction syndrome, multi-organ failure, female sex, use of corticosteroids, severe asthma, ionic abnormalities, malnutrition and immobility are frequently cited causes of CIP and CIM in humans [2,5–7,14,16,18,33,35–38]. As already noted, many of these studies selectively included patients with the risk factor under evaluation, thus precluding a definite answer. In De Jonghe et al.’s systematic review [33] the authors’ conclusion was that there was no strong evidence from clinical studies to support unequivocally a causal relation between sepsis and CIP or CIM. In the prospective, multicenter cohort study from the same group [38], sepsis was not associated with ICU acquired paresis. Hyperglycemia is risk factor for CIP [25]; however, normalization of the serum lipid profile rather than glucose control independently determines the beneficial effects of intensive insulin therapy on morbidity and mortality [59**].

Conclusions

CIP and CIM complicate the clinical course of the most severely ill patients admitted to ICUs. Future studies should better define the clinical characteristics of such patients to make different series comparable, and to define risk factors accurately. Defining a population at risk of developing CIP, CIM or both would be of great interest to patients, since these neuromuscular complications may last for months or years after ICU discharge, causing chronic disability [60–62]. The availability of simplified diagnostic techniques and machines for electrophysiological investigations of peripheral nerves and muscles in the ICU patient would also be welcome.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


29 Van der Meche FG, Van Doorn PA, Meulste J, Jennekens FG. Diagnostic and classification criteria for the Guillain-Barre syndrome. Eur Neurol 2001; 45:133–139.


45 In an experimental model of denervated rat muscle fibers and high-dose steroid, the authors demonstrate that a shift in the voltage dependence of sodium channel fast inactivation to more negative potentials has a crucial role to cause muscle inexcitability.


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