

REVIEW ARTICLE

Critical illness polyneuropathy and myopathy: clinical features, risk factors and prognosis

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Acquired neuromuscular weakness due to critical illness polyneuropathy and myopathy (CIPNM) frequently develops in patients hospitalized in the intensive care unit for more than 1 week. CIPNM may present with muscle weakness and failure to wean from mechanical ventilation, but is discovered more often and earlier by electrophysiological examination. In this review, the incidence, clinical and electrophysiological features, differential diagnosis and prognosis of CIPNM will be described. Risk factors for CIPNM are sepsis or systemic inflammatory response syndrome and the severity of multi-organ failure. Presence of CIPNM is associated with higher mortality rate, prolonged duration of mechanical ventilation and prolonged rehabilitation. The majority of survivors with CIPNM have persistent functional disabilities and a reduced quality of life. There is need for new therapeutic strategies to prevent or minimize CIPNM in critically ill patients.

Introduction

Neuromuscular weakness is often encountered in patients in the intensive care unit (ICU). Patients can be admitted to the ICU because of increasing muscle weakness and threatening respiratory failure due to an underlying neuromuscular disorder, mainly Guillain-Barré syndrome (GBS) and myasthenia gravis. Neuromuscular weakness can also be acquired: it frequently develops in the setting of critical illness in patients admitted to the ICU because of multi-trauma, severe infections, or (multiple) organ dysfunction [1–3]. Neuromuscular weakness in critically ill patients may be caused by a polyneuropathy, myopathy or neuromuscular blockade.

Although polyneuropathy in critically ill patients have been reported in the 1960s and 1970s of the 20th century [4], the first detailed reports of critical illness polyneuropathy were published by Bolton *et al.* and Op de Coul *et al.* [5,6]. All of the reported patients were admitted to the ICU and, during a period of critical illness with sepsis and multi-organ failure requiring artificial respiration, the patients developed a severe sensory-motor polyneuropathy [5–7]. The polyneuropathy was axonal and could therefore be differentiated from the demyelinating form of the GBS [8]. Since these reports, critical illness polyneuropathy has become an increasingly recognized problem affecting both medical and surgical patients in the ICU setting.

Op de Coul *et al.* [9] and especially Latronico *et al.* [10] demonstrated nicely by muscle biopsy that in patients with a clinical and electrophysiological pattern of critical illness polyneuropathy myopathic changes are often present in this patient group, a finding later confirmed by de Letter *et al.* [11]. Even in some patients diagnosed with critical illness polyneuropathy, an underlying myopathy may be the primary cause of the muscle weakness [10–12]. To reflect the difficulty discriminating between myopathic and neuropathic causes of muscle weakness in the ICU, we and others have decided to preferably use the term critical illness polyneuropathy and myopathy (CIPNM) [10–13]. Acute quadriplegic myopathy with selective myosin loss and acute necrotizing myopathy are considered to be a separate entities, as part of critical illness myopathy [14] and will be discussed later (under the heading of differential diagnosis).

Incidence and characteristics

In prospective studies, CIPNM occurs in 25–63% in patients who have been on an artificial respirator for at least 1 week [3,15–20]. This percentage is influenced by the patient population, diagnostic criteria and timing of examination [21] (see also Table 1). In patients with sepsis, this incidence increases to 70–100% [7,22–24]. All age groups are involved, but CIPNM is rare in children. Acquired muscle weakness occurs in 1.7% of critically ill children [25]. Most patients are older than 50 years. Males develop CIPNM about twice as often as females. The reasons for admission to the ICU for patients who develop CIPNM are a variety of medical, surgical and traumatic causes.

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Table 1 Prospective studies in critical illness polyneuropathy and myopathy (CIPNM) evaluating risk factors using a control group

| Author | Year | Population ICU | Total Group on ICU | Group evaluated on occurrence of CIPNM | Diagnosis by | CIPNM (%) | Risk factors | Comments |
|--------------------------------------|-----------|--------------------------|--------------------------------|---|--|--|---|---|
| Leyten <i>et al.</i> [16] | 1995 | Medical-surgical | 368 > 24 h artificial resp. | 50 > 7 days on ICU | EMG on days 7-9, 21, week 8 | 29/50 (58) | Use of aminoglycosides | |
| Thiele <i>et al.</i> [19] | 2000 | After open heart surgery | 1307 | 104 > 3-5 days on ICU 37 enrolled 18 died and excluded | EMG on days 5-7 than weekly (3x), thereafter 2 weeks (4x), 3 weeks | 12/19 (63) | Use of epinephrine/norepinephrine Less use of dobutamine Increased urea | 37 patients enrolled, reason of exclusion of others not clear, risk-factors indicate sepsis and severity of disease |
| Van den Berghe <i>et al.</i> [17,18] | | Mainly surgical | 1548 | | EMG weekly | | Mean blood glucose Vasopressor support | Vasopressor support indicates sepsis |
| Conventional (insulin) treatment | 2001/2005 | | 783 | 206 | | 107/206 (52) 39/206 (19)* 45/157 (29) 11/157 (7)* | Bacteremia Renal replacements | *EMG confirming CIPNM on more than two occasions |
| Intensive (insulin) treatment | | | 765 | 157 > 1 week on ICU | | | | |
| Druschky <i>et al.</i> [24] | 2001 | Medical-surgical | NM | 28 > 4 days on ICU | EMG and clinical evidence of muscle weakness on days 4, 8 and 14 | 16/28 (57) | Age, sepsis, multi-organ failure score on day 8 | |
| Garnacho-Montero <i>et al.</i> [20] | 2001 | Medical-surgical | NM | 82 > 10 days on ventilator with sepsis and MODS 73 included | EMG on days 10 and 21 | 46/73 (63) | Hyperosmolality Parenteral nutrition Use of neuromuscular blocking agents Neurologic failure (GCS below 10) | Nine patients not analyzed Patients with renal replacement therapy lower at risk for development of CIPNM |
| de Letter <i>et al.</i> [15] | 2001 | Medical-surgical | NM | 117 > 3 days on ventilator 11 no informed consent, eight exclusion criteria 98 included | EMG on days 4, 11 and 25 and clinical evidence of muscle weakness | 32/98 (33) | SIRS; Apache III score | Neurologic failure is included in the Apache III score |
| De Jonghe <i>et al.</i> [3] | 2002 | Medical-surgical | 1246 | 332 > 7 days on ventilator 126 exclusion criteria, 111 could not be evaluated i.e. 95 included | Clinical evidence of muscle weakness and EMG | 24/95 (25) | Female sex, number of days with dysfunction of two or more organs Duration of ventilation before awakening Use of corticosteroids | 111 not able to perform reliable clinical examination; early CIPNM and CIPNM in comatose patients not detected MRC score of 4 (out of 5) considered normal SOFA score = severity of multi-organ failure |
| Bednarik <i>et al.</i> [51] | 2005 | Medical | 102 | 61 | EMG and clinical examination | 35 (57) | SIRS; SOFA score | |

NM, not mentioned; ICU, intensive care unit; EMG, electromyological testing; CIPNM, critical illness polyneuropathy and myopathy; GCS, Glasgow coma score; SIRS, systemic inflammatory response syndrome; MRC, Medical Research Council (rating score); resp., respirator.

Diagnosis

Clinical features

The clinical features of CIPNM are distally predominant muscle weakness, muscle wasting, and usually reduced or absent tendon reflexes. Failure to wean from the artificial respirator is common and may be the prevailing symptom of CIPNM. The muscle weakness is most prominent in the lower extremities. If there is reduced limb movement after painful stimulation of the distal limb, limb weakness should be suspected. Facial weakness is rarely present and the discrepancy between a grimace of the facial musculature and decreased limb movement after a painful stimulus is often striking. The exact onset of the muscle weakness can be difficult to determine due to the use of neuromuscular blocking agents or sedatives. Muscle wasting is observed in one-third of the patients [26]. Reflexes usually disappear during the course of the disease, but this is not a prerequisite for the diagnosis. Early in the course of the disease the reflexes are often present [24,27]. Sensory loss can be present, but is often difficult to test in the sedated or intubated patient in the ICU. Thirty percent of the patients have isolated motor symptoms [28]. Impaired consciousness, suggestive of an encephalopathy, is often present, which makes clinical testing of the sensory system even more difficult. Cranial nerve involvement is rare and should be a symptom to search for an alternative neuromuscular disorder.

Laboratory results

Laboratory tests are not diagnostic. Creatine kinase levels are normal or only marginally elevated in most patients with CIPNM [29].

Electrophysiological features

Nerve conduction studies and electromyography are useful for the diagnosis of CIPNM. The electrophysiological changes in CIPNM show both motor and sensory axonal dysfunction of upper and lower extremities [26,30,31]. Electrophysiological testing demonstrates reduction in the amplitudes and increased duration of the compound muscle action potentials within 1 week of onset of CIPNM. Conduction velocities, distal motor latencies and responses to repetitive nerve stimulation are normal. A sensory conduction examination can show decreased sensory nerve action potential amplitudes, which confirms the presence of a polyneuropathy. However, sometimes sensory nerve action potential amplitudes are normal [32]. The sensory nerve action potential can be artificially reduced by

the presence of subcutaneous edema causing a shift of the recording electrode away from the underlying nerve. Tissue edema is typically more often present in the lower limbs. So a decrease in sensory nerve action potential amplitudes in the upper limbs is more suggestive of a polyneuropathy than the presence of decreased sensory responses in the lower limbs.

Fibrillation potentials and positive sharp waves revealed by needle electromyography indicates axonal damage and is more abundant in distal than in proximal muscles. Spontaneous activity is usually present 3 weeks after the start of artificial respiration [8]. However, it can be found within the first 2 weeks [9] or even after 2–5 days after the onset of sepsis [23]. Sometimes there are signs of myopathic changes in the motor unit potentials with a short duration and low amplitudes on voluntary activation. From the electrodiagnostic data, the severity of polyneuropathy can be easily quantified [7].

Is electrophysiology necessary to diagnose CIPNM or is clinical evidence of a polyneuropathy sufficient?

At present, there are no uniform diagnostic criteria for CIPNM. Most studies, retrospective and prospective, used electrophysiological criteria and sometimes also clinical criteria (see also Table 1). The electrophysiological criteria usually have not been described well in these studies.

Morris and Trindler suggested that the clinical finding of muscle weakness is sufficient to diagnose CIPNM [33]. Witt *et al.* [7] found electrophysiological signs of CIPNM in 70% of patients who had sepsis and multi-organ failure. Only 15 of 30 patients (50%) with electrophysiological signs of CIPNM had clinical signs of a polyneuropathy. In the prospective study by Berek *et al.* [22], of 22 patients with sepsis, systemic inflammatory response syndrome (SIRS) or multi-organ failure, nine patients (41%) had clinical signs of a polyneuropathy during their stay in the ICU and seven patients (32%) showed these features 2–3 months later. Electrophysiological examination diagnosed the presence of CIPNM earlier than the clinical investigation. The authors stated that electrophysiological investigation is superior to clinical neurological examination in the detection of polyneuropathies. Leijten and de Weerd [34] found that the sensitivity of the clinical judgment of CIPNM was 60% compared with concurrent polyneuropathy diagnosed with electromyography. De Jonghe *et al.* [3] screened patients in the ICU with at least 7 days on a ventilator daily for awakening and comprehension. On day 7, after persistent awakening and comprehension, muscle strength was evaluated. Muscle weakness could not be evaluated

accurately in 111 of 332 (33%) patients who were at least 7 days on the artificial ventilator. Therefore, with electrophysiological testing, more patients with CIPNM are discovered than by clinical examination alone, and the patients are detected earlier.

Differential diagnosis

An algorithm for the approach to patients with muscle weakness of the limbs in the ICU is shown in Fig. 1 (modified algorithm after Bolton. [35]). A central cause of muscle weakness, such as spinal cord injury or head contusion, must be considered and ruled out by a careful neurological examination with appropriate neuroimaging in every patient with muscle weakness after trauma [2]. In acute spinal cord lesions, the spinal shock may cause weakness of the arms and legs and areflexia, simulating a polyneuropathy. The presence of

ptosis, ocular bulbar weakness, suggests a neuromuscular transmission defect (particularly if variable in time) or a myopathy. Facial weakness should focus the differential diagnosis on a demyelinating polyradiculopathy, myopathy or a neuromuscular transmission defect. Sensory and motor nerve conduction studies, repetitive nerve stimulation and electromyography are the next step in revealing the cause of the neuromuscular weakness. Furthermore, GBS, a treatable inflammatory polyneuropathy, may occur in critically ill patients and electrodiagnostic testing is necessary to differentiate between an axonal or demyelinating neuropathy [8,36]. The presence of a demyelinating neuropathy confirms the diagnosis of GBS and the patients should be treated with immunomodulating therapies. Axonal variants of the GBS exist, but they develop before admission to the ICU and are often associated with a *Campylobacter jejuni* infection and

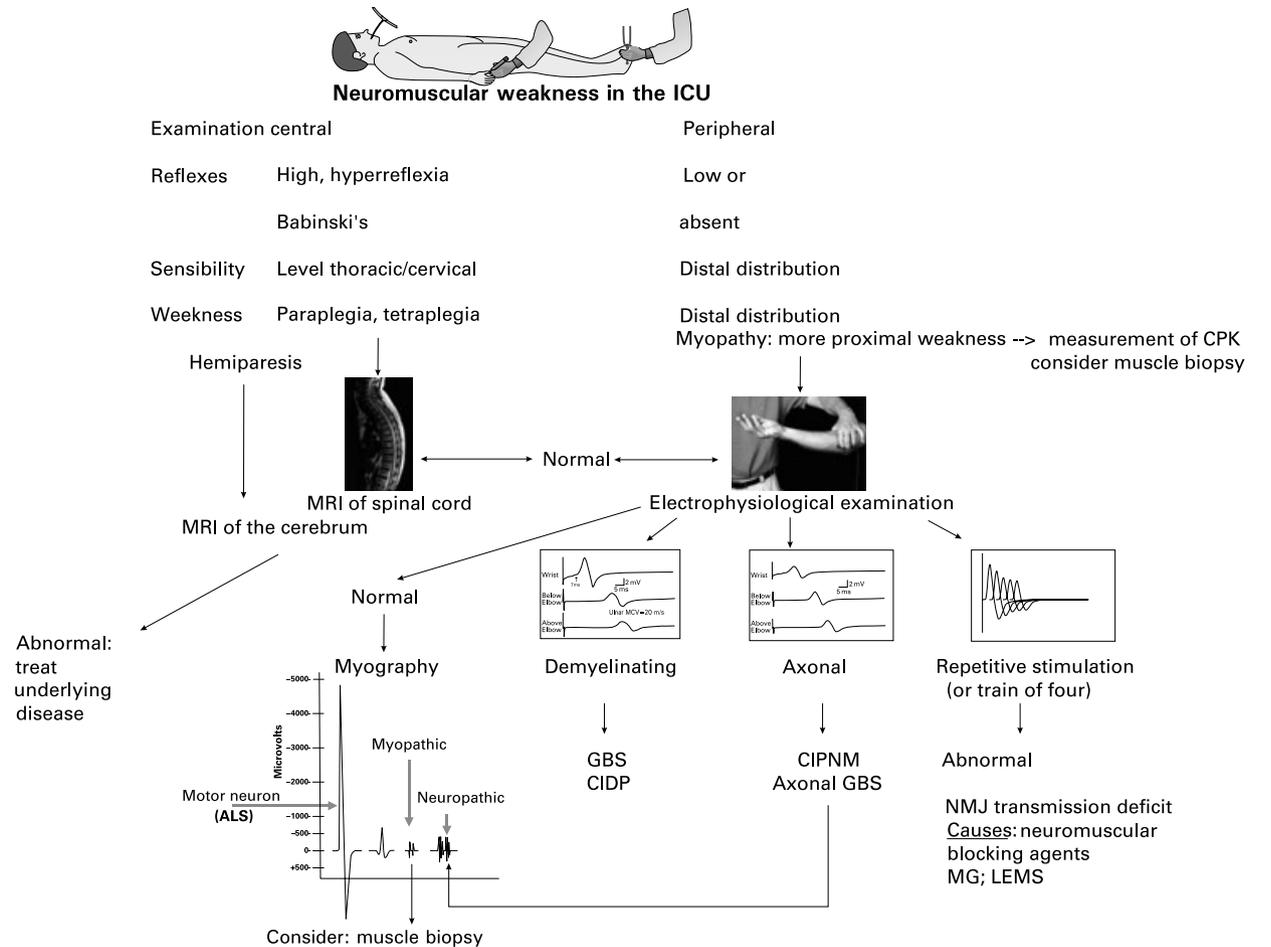


Figure 1 An algorithm for the approach to patients with muscle weakness in the intensive care unit. ALS, amyotrophic lateral sclerosis; CPK, creatine phosphokinase; MRI, magnetic resonance imaging; GBS, Guillain-Barré syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy; CIPNM, critical illness polyneuropathy and myopathy; NMJ, neuromuscular junction; MG, myasthenia gravis; LEMS, Lambert-Eaton myasthenia syndrome. Myopathic pattern: small amplitude and short-duration motor unit potentials, neuropathic pattern: polyphasic motor unit potentials on needle electromyography.

anti-GM1 or anti-GD1a antibodies [37]. Repetitive nerve stimulation studies can be useful when considering the differential diagnosis of CIPNM; these studies are abnormal in patients with defects in the neuromuscular transmission (see Fig. 1).

Neuromuscular weakness may be caused by the use of neuromuscular-blocking agents [38–40]. Risk factors for prolonged neuromuscular blockade in patients in the ICU include hepatic or renal failure, hypermagnesemia, metabolic acidosis and the concomitant use of various antibiotics, especially aminoglycosides and clindamycin [13]. Prolonged neuromuscular blockade is easily detected by repetitive nerve stimulation. Often, train of four is used, which is measurement of the response to four equal pulses over 2 s. Lack of an attenuated response to train of four indicates a prolonged neuromuscular blockade. The neuromuscular blockade can be reversed by giving cholinesterase inhibitors, which are usually short-acting. Prolonged neuromuscular blockade is associated with the development of acute quadriplegic myopathy. This myopathy occurs especially in patients with severe acute asthma, who are treated with a high dose of corticosteroids [14,41], but has also been reported in some critical ill patients who did not receive corticosteroids. In these patients, sensation and reflexes are usually spared. With voluntary muscle activation of weak muscles, electromyographic examination reveals small amplitude and short-duration motor unit potentials (see Fig. 1).

Direct muscle stimulation may help to differentiate between myopathy and neuropathy [42]. In patients with acute quadriplegic myopathy, it has been found that muscles become electrically inexcitable. If the origin of neuromuscular weakness remains unclear, the decision can be made to perform a muscle biopsy. Selective myosin loss in muscle fibers, observed from muscle biopsies, is the pathologic hallmark in these patients [43,44]. Horizontal pore gradient SDS electrophoresis may reveal decreased myosin/actin ratios in percutaneous muscle biopsy specimens in patients with an acute quadriplegic myopathy [45]. In patients with a necrotizing myopathy, creatine kinase levels are elevated [46].

Histopathology of muscle or nerve biopsies in CIPNM

Post-mortem analysis of tissue of patients with CIPNM shows widespread axonal degeneration of both motor and sensory nerve fibers with extensive denervation atrophy of limb and respiratory muscles [30]. In the case of acute denervation, some angular atrophy of isolated scattered muscle fibers is present. However, chronic

denervation shows type-grouping of angular atrophic muscle fibers. Myopathic changes also occur in CIPNM, indicated by the presence of round atrophic muscle fibers, which are interspersed with necrotic muscle fibers [10]. In our prospective study, we performed open biopsy of the quadriceps femoral muscle in 30 patients with CIP [11]. Standard light microscopic examination showed neuropathic changes in 11 (37%) patients, myopathic changes in 12 (40%) patients and both neuropathic and myopathic changes in seven (23%). Muscle fiber necrosis was present in only nine (30%) of the muscle biopsies, showing a sparse and scattered pattern.

Recently, evidence of immune activation in muscle biopsy samples from patients with CIPNM has been found [11]. Helliwell *et al.* [47] found microvascular endothelial activation in the skeletal muscles of patients with multiple organ failure. In our biopsy material, there were either small, clustered infiltrates or presence of isolated inflammatory cells. These cells consisted of macrophages and T-helper 1 cells, not of T-cytotoxic cells or B cells. The vascular endothelium macrophages and T-helper 1 cells showed an activated phenotype (human leukocyte antigen-DR positive), and in the same muscle biopsy samples there was expression of several adhesion molecules on the vascular endothelium. Moreover, MAC-positive staining was seen on the endothelium and on necrotic muscle fibers, when present. Positive staining for pro-inflammatory and anti-inflammatory cytokines was present in the muscle fibers [11].

Fenzi *et al.* [48] were able to perform immunochemical studies of peripheral nerves in critically ill patients and were able to show enhanced expression of E-selectin which occurs on the vascular endothelium of the peripheral nerves.

Risk factors for CIPNM

CIPNM has been attributed to a variety of causes such as parenteral nutrition, autoimmune disorders, gentamycin use, steroid use, use of muscle relaxants, and changes in osmolality. Bolton was the first to suggest that CIPNM was associated with sepsis or SIRS and multi-organ failure [7,49]. In a prospective study, we determined risk factors that contribute to the development of CIPNM. During a follow-up period of 2 years, all patients in the ICU were monitored clinically and electrophysiologically from day 4 of the start of artificial respiration. The occurrence of CIPNM, defined by clinical and electrophysiologic criteria, was related to the Acute Physiology, Age and Chronic Health Evaluation (Apache)-III score and the presence of SIRS [15]. The Apache-III score is a metric that is used to predict

hospital mortality risk for critically ill hospitalized adults [50]. The score is the sum of three groups of variables that relate to physiology, age, and long-term health.

Bednarik *et al.* [51] also recently assessed the risk factors for CIPNM by a prospective follow-up study. They confirmed our findings and found that the presence and duration of SIRS and the severity of multiple and several organ failures were associated with an increased risk of CIPNM.

Other prospective studies evaluating risk factors for CIPNM are shown and summarized in Table 1. From these data, one may conclude that most prospective studies indicate that sepsis and severity of the disease evaluated by the degree of multi-organ failure are risk factors for CIPNM.

Pathogenetic model

In the patients who are critically ill, which is reflected by a high Apache-III score and who have SIRS or sepsis, the host response seems to lead to dysfunction of the neuromuscular system. Severe organ dysfunction, trauma or major surgery may serve as a trigger that induces antigen-presenting cells to produce pro-inflammatory cytokines, such as interleukins 1, 12 and tumor necrosis factor- α (see Fig. 2) [4,15]. This results in activation and influx of mainly T-helper 1 cells,

monocytes, macrophages, and neutrophils. As a result of this immune activation, increased vascular permeability of the endothelial cells occurs. The vascular endothelium controls vasomotor tone and microvascular flow and regulates trafficking of nutrients [52]. The expression of E-selectin and MAC initiates capillary destruction and increases vascular permeability to allow extravasation of inflammatory cells. Extravasation of (inflammatory) cells, edema and hypoxia leads to tissue damage in various systems, including the neuromuscular system, which may be promoted by hyperglycemia and probably also hypoalbuminemia. A disturbed microcirculation with resulting endoneurial edema and hypoxia results in bioenergetic failure which may be responsible for primary axonal degeneration [4].

Prevention and patient care

Controlling glucose

In a study by Van den Berghe *et al.* [17,18] intensive insulin control led to a decrease in CIPNM. Amongst 363 subjects requiring seven or more days of intensive care, the rate of CIPNM defined by electrodiagnostic testing was reduced from 52% to 29%.

Intensive insulin therapy has an anti-inflammatory effect and lowers circulating levels of ICAM and E-selectin levels, improves deranged lipid profile,

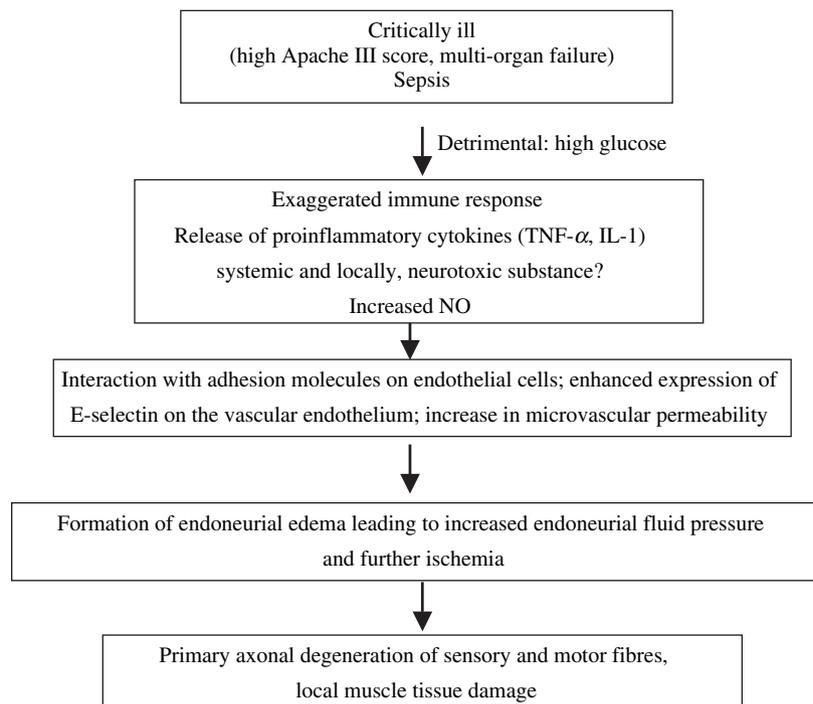


Figure 2 Cascade of pathological changes in critical illness polyneuropathy and myopathy.

Table 2 Studies reporting outcome of patients with CIPNM

| Author | Year | Total population | Selection | No. of patients with CIPNM | Follow-up period | Outcome |
|------------------------------|------|------------------|---|--|---|--|
| Zochodne <i>et al.</i> [30] | 1987 | NM | NM | 19 | NM | 11 (58%) died 8 recovery |
| Witt <i>et al.</i> [7] | 1991 | 43/324 | > 5 days of ICU, sepsis + MOF | 30/43 (15 with clinical signs of polyneuropathy) | 72 (10–190 days) | 23/43 (53%) complete recovery 3/23 with persistent tetraparesis |
| Leyten <i>et al.</i> [16] | 1995 | 72 | 50 with enough EMG data | 29 11 survived | 4 weeks after discharge from ICU and until 1 year | 8 patients moderate to severe weakness: not able to walk more than 50 m without aid at 1 year; severe residual handicap in 5 (22%) |
| Berek <i>et al.</i> [22] | 1996 | NM | 64 Sepsis or SIRS and MOF 41 (64%) excluded | 15/22 (68%) | 3 months | Moderate weakness in 2; mild weakness in 4; no weakness in 9 |
| Hund <i>et al.</i> [27] | 1996 | NM | NM | 7 | 3 months to 3.5 years | 2 died within 8 weeks; 1 full recovery; 2 with mild residual deficits: |
| Latronico <i>et al.</i> [10] | 1996 | NM | NM | 24 | 8–18 months | 1 independent; 1 severe tetraparesis 17 died (14 ICU, 1 in hospital, 2 in rehabilitation center); 7 alive – 1 vegetative state; 6 recovered well or with only moderate disability |
| de Sèze <i>et al.</i> [59] | 2000 | NM | NM (retrospective) | 19 | 2 years | 4 died; 11 complete recovery; |
| Zifko [60] | 2000 | NM | NM | 26 | 13–24 months follow-up of 13 patients (6 died; 7 refused) | paraparesis 1; quadriparesis 3 moderated in 4. Disease had clear effect on quality of life |
| de Jonghe <i>et al.</i> [3] | 2002 | 95 | See Table 1 | 24 | 9 months | 7 died; 12 returned home; 4 long-term care facility, 1 has been lost to follow-up |
| Fletcher <i>et al.</i> [61] | 2003 | 195 | 86 alive; 47 contacted; 25 refused to participate (five ill health or immobility) | 22 | 43 months (range 12–57) | All severe weakness and functional impairments: sensory deficits 6 (27%); only motor weakness in 4 (18%); sensory motor in 3 (14%); 3 upper limb weakness |

ICU, intensive care unit; EMG, electrophysiological testing; CIPNM, critical illness polyneuropathy and myopathy; NM, not mentioned; SIRS, systemic inflammatory response syndrome; MOF, multi-organ failure; MRC, Medical Research Council (rating score).

decreases plasma NO by reducing inducible nitric oxide synthase expression which results in a protection of the endothelium of critically ill patients [52].

Treatment of sepsis

Treatment of sepsis and septic shock are beyond the scope of this review and I refer to the recent management guidelines for severe sepsis and septic shock [53]. It is likely that adequate and early treatment of sepsis will reduce the incidence of CIPNM. There are, however, no prospective studies which support this theory. A retrospective study in patients with sepsis and multi-organ failure who were treated in the early phase of sepsis with intravenous immunoglobulins suggested that this strategy may prevent or mitigate CIPNM [54]. Patients with CIPNM have a higher risk for ventilator-associated pneumonia [20]. Treatment modalities to reduce this risk are centered around the use of semi-recumbent positioning, use of low tidal volume mechanical ventilation, and no or careful use of sedative or neuromuscular-blocking agents [13].

Natural history and prognosis

The prognosis of the polyneuropathy is directly related to the prognosis of the underlying critical illness. Because multiple organ failure is fatal for about 50–60% of the patients, a significant number of patients will die as a result of their underlying illness. Previous reports on the prognosis of CIPNM in patients who survived the intensive care period, have been rather optimistic [7,16,27,30]. The overall mortality rates vary in prospective studies from 36% to 55% [7,15,16,27,30]. The presence of critical illness is associated with a higher mortality rate, prolonged duration of mechanical ventilation and a prolonged rehabilitation [3,16,19,20,55]. CIPNM is probably an additional factor in multi-organ failure and a factor contributing to the persistent severe illness. Garnacho-Montero *et al.* [20] found that the in-hospital mortality was increased sevenfold in the patients who developed CIPNM. Although complete recovery from CIPNM can occur within a few weeks, many patients will need intensive rehabilitation treatment in order to reduce handicaps and achieve optimal autonomy and social participation [56,57].

Regarding long-term follow-up of CIPNM, few data are available and these are summarized in Table 2. Recent data indicate that the majority of survivors have persistent functional disabilities in activities, reduced quality of life and restrictions in autonomy and participation. Follow-up of survivors of the acute respiratory distress syndrome reveals a high prevalence of

persistent weakness and fatigue [58]. These residual symptoms are likely to be due to CIPNM.

In summary, CIPNM is common in critically ill patients. Considering the impact of the disease on physical and social functioning, the related in- and out-hospital costs, new therapeutic strategies should be developed to prevent or minimize the severity of muscle weakness and residual deficits for the increasing number of intensive care patients who develop CIPNM [13].

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