Neuromuscular sequelae of critical illness

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Purpose of review

To investigate the impact of critical illness polyneuropathy and critical illness myopathy on short-term and long-term patient outcome.

Recent findings

In the acute-care setting, critical illness polyneuropathy and critical illness myopathy are important causes of acute paralysis in critically ill comatose patients, and may cause inappropriately pessimistic prognoses. Duration of weaning from artificial ventilation is 2 to 7 times greater in patients with critical illness polyneuropathy than in patients without critical illness polyneuropathy. After intensive care unit and hospital discharge, many patients diagnosed with critical illness polyneuropathy or critical illness myopathy are reported to complain of profound muscle weakness. Chronic disability was a common finding among them. Complete functional recovery with patients regaining the ability to breathe spontaneously and to walk independently was reported in 180 of 263 patients (68.4%); severe disability with tetraparesis, tetraplegia, or paraplegia was reported in 74 patients (28.1%). Persisting milder disabilities were common even in patients with complete functional recovery, and included reduced or absent deep tendon reflexes, stocking and glove sensory loss, muscle atrophy, painful hyperesthesia, and foot drop. An association of critical illness polyneuropathy and critical illness myopathy with increased intensive care unit and hospital mortality has been demonstrated only in selected intensive care unit populations; data are insufficient to demonstrate any association with long-term mortality.

Summary

Intensive care unit-acquired critical illness polyneuropathy and critical illness myopathy influence the evaluation of acutely ill comatose patients and may instigate unreasonably pessimistic prognosis. Critical illness polyneuropathy and critical illness myopathy are an important cause of difficult weaning of patients from the ventilator and of persisting muscle weakness and disability after intensive care unit discharge.

Keywords

chronic disability, coma, difficult weaning, mortality, myopathy, neuropathy

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Abbreviations

CIM	critical illness myopathy
CIP	critical illness polyneuropathy
ICU	intensive care unit
NM-ARF	acute neuromuscular respiratory failure

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Introduction

Critical illness polyneuropathy (CIP) [1] and critical illness myopathy (CIM) [2,3] are neuromuscular sequelae of critical illness that often develop during the intensive care unit (ICU) stay. These neuromuscular abnormalities seem unrelated to a specific etiology. Rather, they have a variety of causes and complicate the clinical course of the most severely ill ICU patients [4].

Development of CIP and CIM may have important consequences for patients since they cause motor and sensory disturbances, which in turn interfere with patient recovery at various stages during both acute-care hospital stay and rehabilitation.

In this review, we discuss the literature describing the impact of CIP and CIM on short-term and long-term patient outcomes.

Definition of critical illness polyneuropathy and critical illness myopathy

Critical illness polyneuropathy is an acute axonal sensorymotor polyneuropathy, mainly affecting the lower limb nerves of critically ill patients [4]. Electroneurography is the gold diagnostic standard [5], since neurologic examination is neither sensitive nor specific [6].

Critical illness myopathy is an acute primary myopathy (that is, not secondary to muscle denervation) whose spectrum extends from pure functional impairment with normal histology to muscle atrophy and necrosis [7]. CIP and CIM often coexist [3], although the diagnosis of CIM in the acute stage of critical illness is by far more complex than that of CIP, requiring specialized electrophysiological investigations or muscle biopsy, and may go unrecognized (see [4] for review).

The occurrence of CIP and CIM varies substantially among different series depending on the diagnostic method used, the patient case mix, and the timing of examination (see [4] for review). The number of patients with CIP and/or CIM discharged from the ICU is, however, small.

Short-term outcome

Problems related to the development of CIP and CIM in the acute stage are seen with proper evaluation of comatose patients and those weaning from the ventilator. A role for CIP as an independent predictor of ICU and hospital mortality is also suggested.

Approach to the comatose patient

'Il movimento è vita' (Movement is life). Luigi Galvani, 1872 [8].

Comatose patients are those not obeying commands, not opening their eyes, nor uttering words despite painful stimulation [9]. In the Glasgow Coma Scale [10], assessment of the reflex motor responses is the only category upon which the consciousness level is based in comatose patients. Therefore, disappearance of motor reflexes has heavy prognostic implications, indicating extensive central nervous system damage. Although careful neurologic examination can differentiate cases in which the motor paralysis is due to central causes from those due to peripheral causes such as CIP and CIM, clinical experience indicates that this is not always the case. Previously, we found that clinicians predicted a fatal outcome in all acutely ill comatose patients developing acute paralysis despite the fact that neurologic signs and physiologic and radiologic investigations did not indicate worsening brain damage [3]. Importantly, when neurophysiological and biopsy investigations revealed CIP and CIM as the cause of paralysis, some patients recovered completely later in the course. Some case reports effectively emphasize the importance of careful investigations and exclusion of CIP and CIM even in the early stage of acute illness [11,12]. Clearly, predicted outcome alters patient treatment [13]. Coma is a potent predictor of mortality and morbidity in a number of acute neurologic diseases [14] and absence of movement in comatose patients is considered a 'deadly' sign. Therefore, exclusion of CIP and CIM can be of primary importance to avoid unreasonably pessimistic prognoses.

Acute neuromuscular respiratory failure

Acute neuromuscular respiratory failure (NM-ARF) leading to ICU admission can be caused by myopathies, neuropathies, and neuromuscular transmission defects [15]. Difficult weaning from the ventilator in patients with no evidence of consciousness disturbances, acute or chronic lung disease, cardiac insufficiency, or persistent sepsis can be due to CIP and/or CIM. In such cases, it can be considered a variety of ICU-acquired NM-ARF.

Difficult weaning from the ventilator has an historical value, since it was the clinical problem that permitted the identification and characterization of CIP in the early 1980s (Table 1) [1]. It was only in 1995 that Maher *et al.* demonstrated acute neuromuscular disorders to be a common cause of difficult weaning. Using electrophysiological studies of the limbs, phrenic nerve conduction, and needle electromyography of the chest wall and diaphragm, they revealed abnormalities in 38 of 40 patients (95%), 19 of whom had CIP. In 1996, Leijten *et al.* [16] found an association between CIP and prolonged mechanical ventilation. In this study, however, *weaning* was not convincingly prolonged. In 2001, Garnacho-Montero *et al.* [17] found that the length of mechanical ventilation was significantly higher in patients with CIP than in patients without (mean (SD) 32.3 (21.1) days *vs* 18.5 (5.8) days, $P = 0.002$). The impact of CIP on difficult weaning from the ventilator was not directly investigated. In 2004, De Jonghe *et al.* [18••] demonstrated that the duration of weaning from mechanical ventilation in patients with ICU-acquired paresis (caused by CIP and/or CIM) was twice that of patients without paresis (mean (range) 6 (0–180) days *vs* 3 (0–146) days, $P = 0.01$). In 2005, Garnacho-Montero *et al.* [19••] showed that the duration of the weaning period was significantly greater in patients with CIP than in those without (median 15 days *vs* 2 days, $P < 0.001$) even after considering other factors suspected to influence the weaning process. Furthermore, 14 of 34 patients (41.2%) with CIP needed reintubation compared with only 4 of 30 patients (13.3%) without CIP. It should be noticed that, with the exception of Maher's study, in no study were the phrenic nerves and the diaphragm evaluated with electrophysiological studies during the ICU stay. The diagnosis of neuromuscular respiratory failure remains therefore speculative, although a significant positive correlation between the involvement of limbs and the diaphragm has been demonstrated [20].

Acute respiratory failure caused by ICU-acquired CIM and CIP may also be revealed after ICU discharge, and has been linked to unplanned ICU readmission and unexpected death [21]. In fact, NM-ARF is a difficult diagnosis to make: dyspnea may be absent, chest x-ray is normal, and arterial blood gases worsen only in the late stage of the disease. The absence of loud wheezing, hypoxia, and hypercapnia may falsely reassure physicians, so that patients are left untreated until overt, life-threatening deterioration appears.

Mortality in the intensive care unit and in the hospital

Two studies found an increased mortality in patients with CIP. In Leijten's study [22] of patients mechanically ventilated more than 7 days, ICU mortality was 48% in patients with CIP and 19% in patients without ($P = 0.03$). Patients were comparable in terms of the Acute Physiology and Chronic Health Evaluation (APACHE II) scores and occurrence of sepsis and multi-organ failure (MOF). However, the authors did not use a validated multi-organ failure scoring system nor did they adjust for potential confounders using multivariable analysis. Interestingly, mortality was no longer significantly different

at 1 year (52% and 43%, respectively, in patients with and without CIP, $P = 0.18$).

Garnacho-Montero *et al.* [17] studied a very select population of patients with sepsis, MOF, and a duration of mechanical ventilation of >9 days. A significant proportion of patients had severe derangement of physiologic variables: 30% had hyperglycemia (blood glucose >250 mg/dl), 60% had hyperosmolality (serum osmolality >325 mosm/kg), 27% had severe acidemia (blood pH < 7.2), and 40% had septic shock. Hospital mortality was higher in patients with CIP than in patients without (84% *vs* 56.5%, $P = 0.01$). The generalizability of these results, particularly after the introduction of intensive insulin protocols [23] (see below), is as yet unproven.

Long-term outcomes

The most frequent physical problems reported by ICU survivors are severe muscle wasting and weakness [24]. Although several case series and cohort studies have shown that CIP and CIM can be responsible for such findings, this association is often overlooked by clinicians and researchers. In a recent paper on survivors of the acute respiratory distress syndrome (ARDS), extrapulmonary conditions were mostly responsible for persistent functional disability [25]. Yet, as Leijten noticed, [26] 'polyneuropathy and myopathy after prolonged intensive care came as a surprise'. Recent retrospective data show that in high-risk patients groups, like those surviving ARDS, as many as 60% (27 of 50) can be found to have CIP and/or CIM [27].

To understand the impact of CIP and CIM on long-term outcomes of critical illness, we reviewed the pertinent literature based on a continuous examination of publications in intensive care, neurologic, rehabilitation, and general medical journals supplemented by a formal MEDLINE search using the following key words: critical illness polyneuropathy, critical illness myopathy, acute quadriplegic myopathy, acute tetraplegia, long-term disability, outcome. Surprisingly, the MeSH database of PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=mesh) describes several types of polyneuropathies, but does not mention CIP. We included studies of adult patients (>18 years old) with a clinical and electrophysiological diagnosis of CIP and/or CIM for whom a follow-up after ICU discharge was reported. Exclusion criteria were case reports and case series with less than 3 patients. Thirty-six studies were included [1,3,5,20–22,28–57], and 51 studies were excluded (list available on request from the authors).

A combined total of 496 patients were reviewed, with long-term outcomes available for 263 patients (53%) (Table 1). Mean sample size was eight patients (SD 7; range 2–32 patients). Mean duration of follow-up was 3–6 months, although the range was quite variable (2 days [49] to 8 years [32]). A wide variety of ICU admission diagnoses were reported, including severe acute respiratory syndrome (SARS) [56]. Difficult weaning from the ventilator, muscle weakness and paralysis, and reduced or absent deep tendon reflexes were the most common signs noted in the ICU; more rarely, sensory signs, neck flexors, and facial involvement were noted (Table 1). Distribution of muscle weakness was symmetric in studies analyzed, although a single case report described a hemiparetic patient with CIM progressing to triplegia [58]. CIP was the most common diagnosis, which was based on standard electrophysiological investigations. Importantly, when biopsy or autopsy investigations were also included, CIM was almost invariably present [3,28,30,34,38,40,41,46–49, 51,54,59]. This suggests that a selective diagnostic bias occurred, since diagnosis of CIM during the acute ICU stay requires muscle biopsy or specialized neurophysiological investigations [4,60,61], which are rarely performed.

Many patients complained of profound muscle weakness after ICU and hospital discharge [55]. Improvement over time was noted in almost all cases and was usually more rapid and complete for the upper limbs and proximal lower limbs followed by respiratory system and finally by distal lower limbs [30]. This observation is in keeping with the demonstration that CIP is a lesion of terminal motor axons [62]. The longer the nerve, the longer it takes for nerve repair and healing, presumably because of the distance separating the nerve terminal from the cellular body, where the machinery for pre-synaptic protein synthesis is mainly located [63]. Data were insufficient to judge whether different electrophysiological diagnoses – CIP, CIM, or both – were associated with different outcomes. In most reports CIP was the main diagnosis associated with persistent disability, while CIM was often associated with rapid and complete recovery. However, incomplete recovery and dismal prognosis were also reported for CIM [51].

Complete functional recovery with patients regaining the ability to breathe spontaneously and to walk independently was reported in 180 patients (68.4%), while severe disability impeding independent walking or spontaneous ventilation was reported in 74 patients (28.1%). In several series the follow-up period was too limited to effectively evaluate recovery. Tetraparesis, tetraplegia, or paraplegia were the most common causes of severe disability. Persisting milder disabilities, including reduced or absent deep tendon reflexes, stocking and glove sensory loss, muscle atrophy, painful hyperesthesia, and foot drop, were common, as were limitations in daily life activities, either objective or perceived [57]. Interestingly, foot drop due to peroneal nerve palsy was usually, but not invariably, bilateral [53]. This suggests that CIP should be considered in the differential diagnosis of foot drop, which is commonly caused by peroneal nerve entrapment at the level of the

Table 1. Long-term follow-up of patients developing critical illness polyneuropathy and/or critical illness myopathy during intensive care unit stay

	Authors (year)	Patients included/ followed-up	Initial clinical findings in the ICU	Diagnostic method(s)	Diagnosis	Duration of follow-up	Functional recovery and outcome after ICU discharge
1	Bolton [1] (1984)	5/2	Difficult weaning from the ventilator, limb weakness, tetraparesis, tetraplegia, reduced or absent DTR, distal sensory loss	Clinical, ENMG, histologic examination (3 pts)	CIP	10 months–2 years	Complete functional recovery: 2 pts 1 pt had normal strength in the face, limb weakness, persistent ventilator dependency at 3 months; at 10 months spontaneous breathing, independent walking; 1 pt in a wheelchair at 4 months; at 2 years independent walking, persistant neuropathy Death: 3 pts (60%)
2	Op De Coul [28] (1985)	12/9	Tetraparesis, reduced or absent DTR, muscle atrophy	Clinical, ENMG, histologic examination (4 pts)	CIP, CIM	5 weeks–5 months	Complete functional recovery: 7 pts (after 2–5 months) Incomplete functional recovery: 2 pts Death: 3 pts (25%)
3	Bolton [5] (1986)	15/6	Difficult weaning from the ventilator, tetraparesis, tetraplegia, reduced or absent DTR	Clinical, ENMG, histologic examination (6 pts)	CIP	10 months–2 years	Complete functional recovery: 6 pts Death:9 pts (60%) Notes: ENMG was unchanged in 3 pts, worsened in 3, improved in 9.
4	Barat [29] (1987)	4/4	Tetraplegia, reduced DTR	Clinical, ENMG	CIP	2 months–2 years	Complete functional recovery: 3 pts (1 pt with reduced DTR) Incomplete functional recovery: 1 pt (in weelchair at 2 years)
5	Zochodne [30] (1987)	19/8	Difficult weaning from the ventilator, tetraparesis, tetraplegia, reduced or absent DTR	Clinical, ENMG, histologic examination (8 pts)	CIP, CIM	10 months–2 years	Complete functional recovery: 8 pts Death: 11 pts (58%) Notes: All 8 survivors had improvement of limb weakness, first in the upper limbs and proximal lower limbs, then in respiratory system, finally in the lower limbs.
6	Gross [31] (1988)	4/4	Global weakness, paralysis, limb pain, bilateral foot drop	Clinical, ENMG	CIP	5 months–2 years	Complete functional recovery: 4 pts 1 pt had persisting pain, 1 pt had persisting disturbance of gait
7	Coronel [32] (1990)	15/4	Limb weakness, muscle atrophy, dysesthesia	Clinical, ENMG	CIP	1–8 years	Complete functional recovery: 3 pts (2 pts had persisting dysesthesia in the lower limbs) Incomplete functional recovery: 1 pt (needing assitance to sit and walk) Death: 5 pts (33%)
8	Partridge [33] (1990)	3/2	Limb weakness, paralysis	Clinical, ENMG	CIP, CIM	5 months to several months	Complete functional recovery: 1 pt (full muscle strength over several months) Incomplete functional recovery: 1 pt (at 5 months supplemental oxygen at home, light housework only, muscle weakness) Death: 1 pt (33%)
9	Apte-Kakade [34] (1991)	4/4	Tetraparesis	Clinical, ENMG, histologic examination (2 pts)	CIM	2–9 months	Complete functional recovery: 4 pts
10	Gooch [35] (1991)	12/10	Limb weakness, paresis and paralysis	Clinical, ENMG, histologic examination (2 pts)	CIP	1–6 months	Complete functional recovery: 8 pts Incomplete functional recovery: 2pts Death: 2 pts (17%)
11	Op de Coul [36] (1991)	22/14	Tetraparesis, reduced or absent DTR, muscle atrophy	Clinical, ENMG histologic examination (7 pts)	CIP, CIM	2 weeks–2 months	Complete functional recovery: 9 pts Incomplete functional recovery: 5 pts Death: 8 pts (36%)

12	Rossiter [37] (1991)	5/3	Tetraparesis, tetraplegia, reduced or absent DTR	Clinical, ENMG	CIP	3 months	Complete functional recovery: 0 pts Incomplete functional recovery: 3 pts 1 pt had persisting tetraparesis and muscle atrophy at 3 months; 1 pt with tetraparesis and muscle atrophy was able to walk with assistance at 5 months; 1 pt with tetraparesis was unable to walk at 1 month Death: 1 pt (20%)
13	Witt [20] (1991)	43/23	Difficult weaning from the ventilator, limb weakness, reduced or absent DTR	Clinical, ENMG	CIP	10–190 days	Complete functional recovery: 20 pts Incomplete functional recovery: 3 pts (tetraplegia, ventilator dependency) Death: 23 pts (53%) (20 pts in the hospital, 3 during follow-up)
14	Griffin [38] (1991)	3/3	Flaccid tetraparesis	Clinical, ENMG, histologic examination (2 pts)	CIM	10 days–3 months	Complete functional recovery: 3 pts
15	Gorson [39] (1993)	5/3	Lim weakness, tetraplagia, reduced or absent DTR	Clinical, ENMG	CIP	4.5–6 months	Complete functional recovery: 0 pts Incomplete functional recovery: 3 pts 1 pt partially dependent on the ventilator, generalized wasting, moderate weakness at 5 months; 1 pt walking with assistance at 6 months 1 pt walking with assistance at 4.5 months Death: 2 pts (40%)
16	Giostra [40] (1994)	9/9	Difficult weaning from the ventilator, tetraparesis, peroneal palsy	Clinical, ENMG, histologic examination (7 pts)	CIP, CIM	24 days–1 year	Complete functional recovery: 6 pts Incomplete functional recovery: 3 pts 2 pts had persistent paresis at 24 and 42 days, respectively 1 pt had persistent peroneal palsy at 1 year
17	Zochodne [41] (1994)	7/3	Weakness, paralysis, opthalmoplegia, absent DTR	Clinical, ENMG, histologic examination (1 pt)	CIM	191–413 days	Complete functional recovery: 2 pts Incomplete functional recovery: 1 pt (bedridden, severe distal wasting, absent DTR, stocking and glove sensory loss) Death: 2 pts (29%)
18	Jarrett [42] (1995)	4/4	Difficult weaning from the ventilator, weakness, foot drop, tetraparesis, peripheral sensory disturbance in a stocking-glove distribution	Clinical, ENMG	CIP	2–5 months	Complete functional recovery: 2 pts (1 pt at 3 months, 1 pt at >5 months) Incomplete functional recovery: 2 pts
19	Leijten [22] (1995)	50/12	Distal paresis, reduced DTR, impaired distal sensation	Clinical, ENMG	CIP	1 year	Complete functional recovery: 7 pts (4 pts recovered within 3 days and 4 weeks, 3 pts within 4 weeks and 1 year) Incomplete functional recovery: 5 pts Death: 9 pts (75%) (4 in the ICU, 5 within 1 year)
20	Souron [43] (1995)	3/2	Tetraparesis, reduced or absent DTR	Clinical, ENMG	CIM, CIP	3–4 weeks	Complete functional recovery: 2 pts (1 in 3 weeks, 1 in 4 weeks) Death: 1 pt (33%)

(*continued*)

Table 1. Long-term follow-up of patients developing critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM) during ICU stay (continued)

	Authors (year)	Patients included/ followed-up	Initial clinical findings in the ICU	Diagnostic method(s)	Diagnosis	Duration of follow-up	Functional recovery and outcome after ICU discharge
21	Berek [44] (1996)	22/15	Difficult weaning from the ventilator, muscle weakness, tetraplegia, reduced DTR	Clinical, ENMG	CIP	2–3 months	All pts improved Complete functional recovery: 9 pts Incomplete functional recovery: 6 pts 4 pts had mild weakness, 2 pts had moderate weakness, 5 pts had muscle atrophy; DTR were reduced in 6 pts and absent in 1. Death: 7 pts (32%)
22	Hund [45] (1996)	7/3	Difficult weaning from the ventilator, tetraparesis	Clinical, ENMG	CIP	3 months–3.5 years	Complete functional recovery: 2 pts Incomplete functional recovery: 1 pts (slight tetraparesis) Death: 2 pts (29%)
23	Lacomis [46] (1996)	14/10	Difficult weaning from the ventilator, generalized severe limb weakness, neck flexors and facial weakness, reduced or absent DTR	Clinical, ENMG, histologic examination (14 pts)	CIM	1 week–12 months	Complete functional recovery: 5 pts (at 1 week, 2, 2, 3, and 12 months, respectively) Incomplete functional recovery: 5 pts 3 pts were walking with assistance at 6 weeks, 3 and 4 months, respectively; 1 pt had moderate weakness at 2 months, 1 pt was ventilator-dependent at 2 months Death: 2 pts (14%)
24	Latronico [3] (1996)	24/7	Tetraparesis, tetraplegia, reduced or absent DTR	Clinical, ENMG histologic examination (24 pts)	CIM, CIP	8–18 months	Complete functional recovery: 6 pts Incomplete functional recovery: 1 pt (in a vegetative state) Death: 17 pts (71%)
25	Rich [47] (1996)	3/3	Tetraplegia, absent DTR	Clinical, ENMG, histologic examination (1 pt)	CIM	2–3 months	Incomplete functional recovery: 3 pts
26	Hanson [48] (1997)	4/3	Tetraplegia, absent DTR	Clinical, ENMG, histologic examination (4 pts)	CIM	2–8 months	Complete functional recovery: 3 pts (within 2, 5, and 8 months), Death: 1 pt (25%)
27	Campellone [49] (1998)	8/4	Generalized weakness (including neck flexors), facial paresis, reduced DTR, difficult weaning from the ventilator	Clinical, ENMG, histologic examination (5 pts)	CIM	2 days–12 weeks	Complete functional recovery: 3 pts Incomplete functional recovery: 1 pt (within 4–12 weeks) Death: 2 pts (25%)
28	Inser-Horobeti [50] (1998)	4/4	Muscle weakness and atrophy, tetraparesis, absent DTR	Clinical, ENMG	CIP, CIM	6–8 months	Complete functional recovery: 1 pt Incomplete functional recovery: 3 pts (severe disability, dependence in daily life activities)
29	Lacomis [51] (1998)	92/32	Difficult weaning from the ventilator, tetraparesis, tetraplegia, distal sensory loss	Clinical, ENMG histologic examination (22 pts)	CIM, CIP	3–12 months	Complete functional recovery: 25 pts 17 pts were ambulatory within $<$4 months; 8 pts were ambulatory within 4–12 months Incomplete functional recovery: 7 pts 4 remained non ambulatory; 3 remained dependent on the ventilator Death: 16 pts (31%)
30	Latronico [21] (1999)	4/4	Not reported	Clinical, ENMG	CIP, CIM	3–6 months	Complete functional recovery: 3 pts within 3, 5, and 6 months) Incomplete functional recovery: 1 pt (at 5 months able to walk with assistance; ataxic)

31	De Sèze [52] (2000)	19/15	Difficult weaning from the ventilator, tetraparesis, reduced DTR	Clinical, ENMG	CIP	3 months–2 years	Complete functional recovery: 11 pts within 3 months (4 pts), 6 months (4 pts), 1 year (3 pts) Incomplete functional recovery: 4 pts 2 paraparesis, 2 paraplegia at 2 years Death: 4 pts (21%)
32	Zifko [53] (2000)	26/13	Not reported	Clinical, ENMG	CIP	13–24 months	Complete functional recovery: 2 pts Incomplete functional recovery: 11 pts 6 pts had polyneuropathy, 4 had mononeuropathy and 1 had both. Muscle weaknes was severe in 1 pt, mild in 8;sensory abnormalities (painful hyperesthesia, hypaesthesia) were present in 10 pts; peroneal nerve palsy in 4 pts (1 bilateral, 3 unilateral); reduced or absent DTR in 5 pts; walking with devices in 5 pts. Death: 6 pts (23%) (2 in the ICU, 4 pts within the first year after CIP)
33	De Jonghe [54] (2002)	24/16	ICU-acquired paresis	Clinical, ENMG, histologic examination (10 pts)	CIP, CIM	9 months	Complete functional recovery: 12 pts Incomplete functional recovery: 4 pts Death: 7 pts (29%) Notes: In half of pts ICU-acquired paresis resolved within 3 weeks
34	Fletcher [55] (2003)	22/22	Not reported	Clinical, ENMG	CIP	12–57 months	Complete functional recovery:20 pts 6 pts had sensory deficits, 4 pts had motor weakness, 3 pts had combined sensory and motor deficits, 2 pts had bilateral peroneal nerve palsy with foot drop, 3 pts had bilateral upper limb weakness Incomplete functional recovery: 2 pts Notes: all patients and extreme weakness after ICU and hospital discharge.
35	Tsai [56] (2004)	4/4	Paraparesis, tetraparesis, distal sensory loss, reduced DTR	Clinical, ENMG	CIP, CIM	7 weeks–3 months	Complete functional recovery: 4 pts (two pts within 7 weeks, and two within 2 and 3 months) 1 pts had persisting impairment of distal sensation and reduced DTR
36	Van der Schaaf [57] (2004)	16/5	Not reported	Clinical, ENMG	CIP	6–12 months	Complete functional recovery: 1 pt Incomplete functional recovery: 4 pts Pts were independent in self-care and basic daily life activities, but needed devices to walk Death: 9 pts (56%)

Complete functional recovery, patients able to breath spontaneously and to walk unassisted; Incompete functional recovery, patients dependent on the ventilator or walking with assistance; CIP, critical illness polyneuropathy; CIM, critical illness myopathy; ICU, intensive care unit; ENMG, electroneurography, electromyography; Pts, pt, patient(s); DTR, deep tendon reflexes.
Study No. 5 (Zochodne, 1987) includes 17 patients from previous studies (2 patients of study No. 1 and 15 patients of study No. 3).
Study No. 11 (Op de Coul, 1991) includes 12 patients of study No. 2.
Study No. 29 (Lacomis, 1998) includes 9 patients of study No. 23.

fibula head and is usually attributed to nerve stretching and/or compression due to patient malposition.

Average mortality among these patients was 23.8% (standard deviation 22; range 0–75%). Importantly, mortality was evaluated in the ICU in some series and in the hospital or at variable time during follow-up in others. Three additional considerations limit interpretation of the mortality data: first, only patients with CIP or CIM were followed and controls were not included; second, other prognostic variables were not taken into account (e.g., clinical severity, admission diagnosis, age, co-morbidities, etc.); third, sample sizes were small.

Prevention and treatment

More than 50 drugs [2], notably neuromuscular blocking agents (NMBAs) and aminoglycosides, may alter *neuromuscular transmission*, thereby causing pharmacological muscle denervation. Muscle denervation causes a marked upregulation of acetylcholine receptors [64]. These latter are normally located at the crest of the folds of the postjunctional end-plate at a concentration greater than 1000 times that of extra-junctional sites on the muscle membrane. With upregulation new receptors are spread throughout the muscle membrane. The receptor increase in the peri-junctional area causes resistance to nondepolarizing NMBAs, while the overall increase may result in hyperkalemia after depolarizing NMBAs, such as succinylcholine. Denervation also causes a rise of glucocorticoid receptors in the cytosol of skeletal muscle, which results in an increased sensitivity of the muscle to steroids [65]. Current recommendations are that NMBAs should be used in selected situations such as to treat difficult-to-ventilate patients, reduce intracranial pressure, treat muscle spasms, and decrease oxygen consumption only when all other means have been tried without success [66]. Daily NMBAs interruption is also recommended to reduce the risks associated with prolonged pharmacological denervation [66]. No formal recommendations exist for succinylcholine, which is rarely used in the ICU. We would discourage its use in patients with suspected (i.e., patients with prolonged ventilator dependency or with flaccid paralysis not related to primary disease) or proven CIP and/or CIM due to the risk of hyperkalemic cardiac arrest [2,64,67].

Several electrolyte abnormalities, including hypokalemia and hyperkalemia and hypophosphatemia, may damage the muscle and should be treated vigorously. Among drugs, propofol, catecholamines, and corticosteroids deserve special attention. Propofol uncouples oxidative phosphorylation and energy production in the mitochondria and may cause a so-called propofol-infusion syndrome characterized by severe metabolic acidosis, rhabdomyolysis, renal failure, and fatal cardiac failure when used at doses higher than 5 mg/kg/h for prolonged periods (>48 hours) [68]. Catecholamines can lead to muscle injury indirectly, by increasing cardiac output and propofol requirements, and directly, by damaging the myocyte [68]. Chronic corticosteroid use is long recognized as a cause of muscle damage [69,70]. Only recently it has been demonstrated that corticosteroids are an independent risk factor for ICU-acquired paresis [54]. Interestingly, catecholamines and steroids are also the two major end-products of the stress response, which explains why critically ill neurologic patients are at increased risk of developing cardiac and peripheral muscle damage [68]. It is thought that propofol, catecholamines, and corticosteroids act as triggering factors of acute muscle damage, with 'critical illness' being the priming factor [68]. Therefore, their use should be based on precise indications. In patients with acute neurologic or inflammatory illnesses, alternative sedative agents to propofol should be considered [66,68]. Use of corticosteroids should be restricted to conditions such as septic shock [71••], adult meningitis [72], unresolved acute respiratory distress syndrome [73], severe community-acquired pneumonia [74••], and status asthmaticus [75], in which corticosteroids have been shown to have a significant impact on morbidity and mortality.

No specific treatments exist for CIP and CIM. Strict blood glucose control has been shown to reduce the occurrence and duration of CIP [23]. Intensive physiotherapy also seems promising [21,57], although larger studies with better methodological quality are needed. It is not known if polyclonal immunoglobulins, which benefit a number of acute and chronic autoimmune polyneuropathies [76,77], will play a role in the management of CIP [78,79]. Ongoing studies may shed light on this topic in the near future.

Conclusion

Only limited evidence is available suggesting that CIP increases ICU and hospital mortality in critically ill patients. Concerning long-term mortality after hospital discharge, data are largely insufficient to demonstrate any role for CIP and CIM. Conversely, evidence indicating that CIP and CIM are important causes of increased morbidity during and after acute-care hospital stay is more consistent. Duration of follow-up was limited in many cases, leaving unsettled the question of whether deficits following CIP and CIM are persistent.

Sensible targets for future clinical research in the *acute* setting would be whether prevention and active treatment of CIP and CIM reduce the duration of mechanical ventilation and weaning as well as the number of ICU readmissions and post-ICU unexpected deaths. Future studies aimed at describing *long-term* outcome should rely on longer follow-up time, presumably 3 years or more [53]. Since CIP and CIM only affect a minority of ICU patients [4], a prospective cohort study to define long-term prognosis

would be difficult [80]. Other more cost-efficient and time-efficient study designs, such as a multi-center retrospective cohort study or a nested case-control study [81] may prove useful.

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