Treatment of critical illness polyneuropathy and/or myopathy – a systematic review

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ABSTRACT

INTRODUCTION: The objective was to search the literature with a view to providing a general description of critical illness myopathy/polyneuropathy (CIM/CIP), including its genesis and prevention. Furthermore, it was our aim to determine whether new treatments have occurred in the past five years.

METHOD: PubMed, CINAHL and Swedmed+ were searched using the terms CIM, CIP and intensive care. The search was narrowed by adding the limits: humans, English, Danish, Norwegian, Swedish and, furthermore, articles had to have been published in the past five years as we aimed to focus on new knowledge.

RESULTS: A total of 74 articles were found. We excluded articles focusing on children and intensive care, tight insulin therapy in patients without CIM/CIP and articles focusing on Guillain-Barré syndrome, triage, bleeding, alcohol or meningitis. Of the remaining 36 articles, only five focused on CIM/CIP treatment. Their relevant original references were found and used too.

CONCLUSION: CIM/CIP is the most commonly occurring intensive care unit (ICU)-acquired neuromuscular dysfunction, and it is associated with a significant increase in length of stay, delayed weaning from mechanical ventilation, prolonged rehabilitation and, consequently, more expenses. To treat/prevent this condition, it seems reasonable to ensure maximal functional status for survivors of an ICU-stay by applying a multimodal therapeutic approach that includes intensive insulin therapy, minimal sedation and, as suggested by new evidence, early physiotherapy and electrical muscle stimulation.

ABBREVIATIONS

6MWD = 6 min walking distance
ARDS = acute respiratory distress syndrome
CHF = chronic heart failure
CIM = critical illness myopathy
CIP = critical illness polyneuropathy
CIPNM = critical illness polyneuromyopathy
COPD = chronic obstructive pulmonary disease
EMG = electromyography
EMS = electrical muscle stimulation
ICU = intensive care unit
IIT = intensive insulin therapy
MIP = maximal inspiratory pressure
MOF = multiorgan failure
MRC = Medical Research Council
MV = mechanical ventilation
OR = odds ratio
PROM = passive range of movement
RCT = randomized clinical trial
SBP = spontaneous breathing periods
SIRS = systemic inflammatory response syndrome

SYSTEMATIC REVIEW

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Critical illness myopathy (CIM) and/or critical illness neuropathy (CIP) is a frequent and serious complication to intensive care that delays weaning from mechanical ventilation (MV), increases the length of stay at the intensive care unit (ICU), compromises rehabilitation and may result in a lifelong loss of function and in a reduction in quality of life [1-15].

CIM is an acute primary myopathy and is defined by loss of thick filament myosin and Type II fiber atrophy, mainly with proximal weakness [12, 14-16] and maybe reduced muscle fibre excitability [17]. CIP is caused by axonal degeneration of both the motor and sensory nerve fibres (sparing the cranial nerves and autonomic functions), which results in primarily distal weakness [15]. Both CIP and CIM affect the deep tendon reflexes and cause distal weakness with facial musculature often being strikingly spared [14, 18].

Although advancements in critical care have led to improved survival, these have also led to longer periods of support in the ICU for those who are most seriously ill. The incidence and detection of acquired neuromuscular disorders have consequently increased. Even without CIM/CIP, bed rest for only one week will reduce muscle bulk by up to 30% [19]. The reduction of muscle bulk is higher in the first 2-3 weeks of the ICU stay [20].

The aim of this review was to search the literature with a view to providing a general description of CIM/CIP, including its genesis and prevention. Furthermore, it was our aim to determine whether new treatments have occurred in the past five years.

METHOD

PubMed, CINAHL and Swedmed+ were searched for articles using the following criteria: humans, English, Danish, Norwegian, Swedish and, furthermore, articles had to have been published in the past five years to focus on new knowledge. Two search terms were used: (CIM OR “critical illness myopathy”) AND (“intensive care” OR ICU) and (CIP OR “critical illness polyneuro-

pathy") AND ("intensive care" OR ICU). PubMed returned 56 articles, CINAHL 18 articles and Swedmed+ returned none. We excluded articles not focusing on CIM/CIP (articles focusing on children and intensive care, articles focusing on tight insulin therapy in patients without critical illness polyneuropathy and articles focusing on Guillain-Barré syndrome, triage, bleeding, alcohol or meningitis). Of the remaining 36 articles, only five focused on CIM/CIP treatment (**Table 1**) [13-16, 21]. If needed, their relevant original references were found and used, too (**Figure 1**).

RESULTS

Cause, definition and risk factors

It has long been known that patients admitted to the ICU often subsequently develop reduced neuromuscular function [22]. Electrophysiologic studies on motor and sensory nerve conduction, but also studies on electromyography in the limbs, have defined two broad categories of acquired neuromuscular dysfunction: CIP and CIM; but a significant overlap often exists which has given rise to the use of the term "critical illness polyneuromyopathy" (CIPNM) [16, 23]. One study found that out of 55 consecutive patients with a critical illness 18, 16 and nine patients had CIM, CIP and CIPNM, respectively [23].

The causes of CIM and CIP are still not fully understood. Several risk factors have been identified with varying degrees of evidence. The risk factors include the severity and duration of systemic inflammatory response syndrome (SIRS) [15, 24-26], sepsis, a high acute physiology and chronic health evaluation (APACHE) III score [15, 25], the number of organ failures [15, 24], hyperglycaemia [7, 27, 28], immobility [16], low serum albumin [7, 28], female sex [29], parenteral nutrition [8] and, possibly, the use of steroids [15, 25, 26, 29, 30] or neuromuscular blocking agents [8, 15, 25, 26], although there are conflicting reports in regards to steroids and neuromuscular blocking agents [1, 5, 6, 9-11, 16, 18, 29, 31, 32].

One study comparing sepsis and multiorgan failure (MOF) patients with healthy volunteers, showed that CIPNM, rather than immobilization, is the cause of muscle weakness [33]. But during the ICU stay, the natural loss of muscle bulk may further complicate the condition. Other studies showed a correlation with serum endotoxin, interleukin-2-receptors and the severity of CIP [28] or that raised potassium and hypoperfusion causes depolarization of the motor neurons and possibly neuropathy [34]. Insulin-like growth factor binding protein 1 is also correlated to the development of CIPNM [26]. Interestingly, one study has shown a protective effect of renal replacement therapy [8].

TABLE 1

The five main articles.

Reference	Study design	Evidence level[a]	New treatment strategies	Results	Strength and limitations
Routsi et al, 2010 [21]	Randomized controlled trial (n = 140) Electrical muscle stimulation group (n = 68), control group (n = 72)	2B (do not include follow-up)	Assess the efficacy of EMS (55 min) in preventing CIPNM MRC used to diagnose CIPNM was diagnosed in three patients in the EMS group and in 11 patients in the control group (OR = 0.22, p = 0.04)	The MRC score was higher in the EMS group than in the control group (58 versus 52, p = 0.04) and the ICU stay was shorter in the EMS group (14 versus 22 days) Those patients who developed CIPNM had a prolonged long-term weaning period, 12 versus 1 day(s) (p = 0.0001) and a longer ICU stay 25 versus 11 days (p = 0.01)	EMS session can prevent the development of CIPNM, shorten duration of MV and length of stay in critically ill patients EMS session was not used in the control group
Doherty & Steen, 2010 [13]	Review 84 references	5	Early mobilization in critical care using passive range of movement exercise	The literature indicates early physical therapy in critical care could improve patients' functional capacity, improve recovery time, promote early weaning and discharge from intensive care unit	Structured rehabilitation programme There is no general agreement or evidence-based guidance on the intensity, frequency and duration of such physical therapy
Ricks, 2007 [15]	Review 36 references	5	Focus on implications for weaning and rehabilitation	Exclude other causes of delay of weaning, treatment of the underlying cause and facilitated early physiotherapy	Exclusion of other neuromuscular dysfunction Lack of long term prospective studies on outcome measurements in follow-up studies
Schweickert & Hall, 2007 [16]	Review 69 references	5	Examination using MRC scale Identifies common risk factors	MRC reliability Using protocol to minimized risk factors	Oedema is not an impediment for MRC Examination dependents on patient's cooperation
Robinson, 2006 [14]	Review 17 references	5	History of CIM/CIP, diagnosis and physical therapy management are discussed	No definitive medical treatment is available to prevent CIM/CIP Avoidance of SIRS Rehabilitation	Early rehabilitation Incidence rates depend on population character, and study design

CIM = critical illness myopathy; CIP = critical illness polyneuropathy; CIPNM = critical illness polyneuromyopathy; EMS = electrical muscle stimulation; ICU = intensive care unit; MRC = Medical Research Council; MV = mechanical ventilation; OR = odds ratio; SIRS = systemic inflammatory response syndrome.
a) Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009), www.cebm.net.

Diagnosis

The occurrence of the condition varies depending on the case mix, the diagnostic method used and the timing of the examination. Studies restricted to patients with sepsis and MOF have found that between 50% and even up to 100% of the patients develop signs of CIPNM [11, 35]. However, CIPNM often remains undetected in clinical practice [13, 36, 37].

The diagnosis is currently made by neurophysiological examination (electromyography (EMG) and nerve conduction) and biopsy is rarely necessary [23]. The Medical Research Council (MRC) scale for muscle examination (< 48 of 60 points) has been used, but does not state the origin of the weakness [16]. It may, however, be an effective screening tool and a help in quantifying and monitoring the development of weakness in awake and cooperative patients. The MRC is a publicly funded government agency responsible for co-ordinating and funding medical research in the United Kingdom. It has also been suggested to use a simplified screening examination of EMG and nerve conduction (sensitivity 100% and specificity 67%), using only two nerves in one leg. This approach reduces the examination time from 45-90 minutes to 5-10 minutes [38, 39]. The diagnosis of CIPNM can often be made as early as two days after admittance [16, 30], which suggests that the damage is caused very early in the ICU stay.

When a neuromuscularly weak patient who cannot be weaned from MV is encountered, it is important to remember that multiple causes may co-exist, and it is important to rule out other causes than CIPNM [15, 40].

Prevention/therapy

Prevention of risk factors and treatment of the underlying critical illness as well as ICU supportive care are mandatory [16, 41]. Presently, there are four methods by which CIPNM may be treated or prevented: a) intensive insulin therapy (IIT), b) minimal sedation, c) physiotherapy and training, d) electrical muscle stimulation.

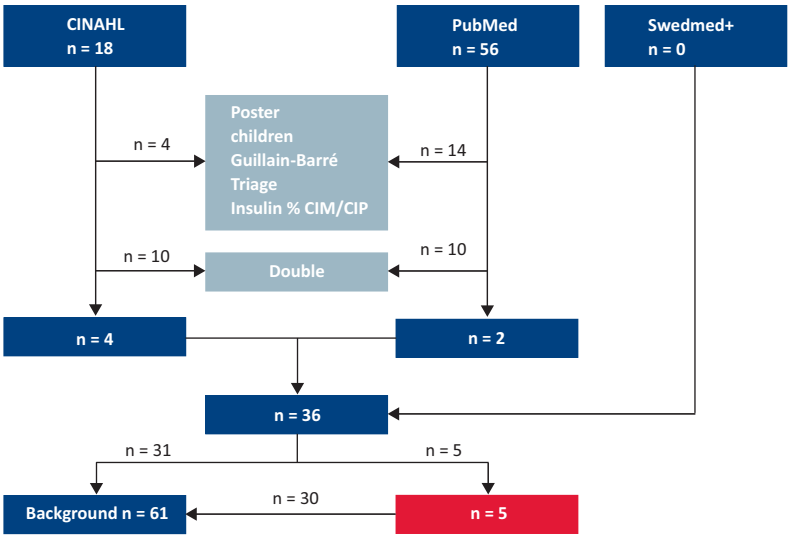
Intensive insulin therapy

A large randomized clinical trial (RCT) from 2001 involving 1,548 surgical ICU patients which was designed with CIP as an outcome measure showed that IIT was associated with a 34% reduction in overall hospital mortality plus a 44% reduction in patients diagnosed with CIP; and when CIP did occur, the condition also resolved more rapidly in the IIT group. The patients were also less likely to receive prolonged mechanical ventilation and intensive care [42-44]. A reduction in mean blood glucose from 159 to 102 mg/dl, or from 144 to 107 mg/dl or a blood glucose level between 80-110 mg/dl have been shown to yield the best effect [31, 43, 44]. IIT has no survival benefits on patients with a prior history of diabetes [45]. When data were pooled with those of a study involving medical ICU patients, it was found that the odds ratio (OR) for developing CIPNM was 0.49 ($p < 0.0001$) among patients treated with IIT [45].

A study of 420 medical ICU patients with mechanical ventilation for at least seven days showed that IIT reduced the incidence of CIPNM from 50.5% to 38.9% ($p = 0.02$). Also MV ≥ 14 days was reduced from 46.7% to 34.6% ($p = 0.01$) [43]. When IIT was implemented in two ICUs (168 patients before and 452 after implementation), it still reduced the diagnosed CIPNM in screened long-stay patients from 74.4% to 48.7% ($p < 0.0001$). The OR for prolonged MV for the IIT patients was 0.49 [44].

FIGURE 1

Flow diagram.



CIM = critical illness myopathy; CIP = critical illness polyneuropathy.

Minimal sedation

Daily interruption of sedative drug infusion has not been studied in relation to CIP/CIM; but it has been shown to decrease the duration of MV (4.9 versus 7.3 days) and the duration of the ICU stay (6.4 versus 9.9 days) in an RCT involving 128 MV-ICU patients [46]. The use of a sedation protocol reduces MV time (55.9 versus 117 hours), ICU stay (5.7 versus 7.5 days) and hospital stay (14 versus 19.9 days) and lowers the rate of tracheostomy (10 versus 21 patients) [47]. Although this might not actually treat CIPNM, it still influences respiratory training and reduces the immobilization and thus the loss of muscle bulk [19, 20]. Management of ICU delirium may further contribute to early mobilization and active training [13].

Physiotherapeutic training during ambulation from intensive care unit (constructed).

Physiotherapy and training

A pre-post cohort study including 104 patients who required MV for > 4 days and were transferred from an ICU to a respiratory ICU showed that applying an early activity protocol significantly increased the probability of ambulation, regardless of the underlying pathophysiology. The authors concluded that the ICU environment may contribute unnecessarily to immobilization. Sedatives, even given intermittently, substantially reduce the likelihood of ambulation. This study did not describe the number of CIPNMs [48].

In an RCT involving 80 patients with chronic obstructive pulmonary disease (COPD) and acute respiratory failure, 61 patients were mechanically ventilated upon admission to the unit. The patients in group A (n = 60) received pulmonary rehabilitation containing passive and active mobilization plus standard medical therapy, and the patients in group B (n = 20) received standard medical therapy. The total lengths of ICU stay were shorter in group A than in group B (33.2 versus 38 days). At discharge, the 6-min walking distance (6 MWD) ($p < 0.001$) as well as the maximal inspiratory pressure (MIP) ($p < 0.05$) were better in group A. CIPNM was not evaluated in this study [49].

Another RCT included 90 critically ill patients in two groups, who were included as soon as their cardiorespiratory condition allowed bedside cycling exercise (starting from day 5), given they still had an expected prolonged ICU stay of at least seven more days. Both groups received respiratory physiotherapy and a daily standardized passive or active motion session of the upper and lower limbs. In addition, the intervention group performed a passive or active exercise training session for 20 min/day using a bedside ergometer. At hospital discharge, 6MWD, isometric quadriceps force and the subjective feeling of functional well-being were significantly higher in the intervention group ($p < 0.05$) than in the non-intervention group. CIPNM was not described, but the use of corticosteroids and neuromuscular blocking agent was evaluated [20].

Furthermore, in a study including 39 patients who were expected to need MV for more than 14 days, the patients in the intervention group (n = 20) participated in a rehabilitation programme administered five days a week for six weeks by a physiotherapist. The programme consisted of exercises for the upper and lower limbs using weights, breathing exercises for respiratory muscle and functional activities. The control group (n = 19) received standard treatment. After six weeks, respiratory and limb muscle strength were significantly improved in the intervention group. Also the Barthel index of activities of daily living [50] and the functional independence measure improved significantly. CIPNM was not evaluated, but the study excluded patients with comorbid medical conditions (e.g. neurological diseases) or who were treated with any sedative or paralytic agents that would interfere with strength measurements and limb exercises [51].

A prospective cohort study included 330 MV ICU patients who were identified prospectively and enrolled within 48 hrs of intubation and 72 hrs of admission to the ICU. The protocol patients (n = 165) received usual treatment plus treatment according to a mobility protocol starting after 48 hours of MV. The protocol treatment was instructed by a mobility team consisting of a critical care nurse, a nursing assistant and a physiotherapist. The protocol exercises started with passive range of movement (PROM) and when the patients began to show progress, the exercises focused on functional activities. The usual care group (n = 165) received usual treatment, including physiotherapy, administrated by the nurse practicing PROM during bedside care. The protocol group was out of bed earlier (five versus 11 days) than the control group, had a reduction in ICU stay (5.5 versus 6.9 days) and a reduction in hospital stay (11.2 versus 14.5 days). Moreover, there was no cost difference between the two groups. CIPNM was not evaluated [52].

Immobilization secondary to sedation may potentiate the weakness from CIPNM. A RCT involving 104 patients on MV for less than 72 hours and who were expected to continue for at least 24 hours showed that daily interruption of sedation including physical and occupational therapy reduces the duration of delirium (2 versus 4 days) and results in more ventilator-free days (23.5 versus 21.1 during the 28-day follow up) compared with daily interruption of sedation only [53].

A prospective, randomized controlled study en-

rolled 66 patients into either supported arm training plus general physiotherapy (n = 32) or to general physiotherapy alone (n = 34). When the patient was weaned from MV, supported arm training turned out to improve muscle fatigue and isotime dyspnoea as well as post-training MIP [54].

A small descriptive study of five patients with MV and a neuromuscular block for seven days showed that three hours of passive leg stretching per day preserves the architecture of muscle fibres and prevent atrophy [55]. A descriptive study of ten patients showed that inspiratory muscle strength training in combination with progressive spontaneous breathing periods (SBP) facilitate the weaning of patients from MV [56].

Electrical muscle stimulation

Electrical muscle stimulation (EMS) has been used as an alternative to active exercise in patients with chronic heart failure (CHF) and in COPD patients (not ICU patients) because even the clinically stable patients experienced severe dyspnoea which prevented the regular application of active training [57]. EMS has been shown in many studies to improve muscle mass [58], muscle strength, exercise capacity and/or health status [59], and EMS was well tolerated [58]. Furthermore, EMS probably reduces muscle catabolism and improves the microcirculation in ICU patients [60, 61].

An RCT including 24 patients with COPD receiving MV showed that EMS sessions of 30 minutes in 28 days significantly improves muscle strength and decreases the number of days needed before the patients were able to transfer from bed to chair. The technique was well tolerated and improved the patients' quality of life. The authors found that that EMS was safe, inexpensive and reliable. CIPNM was not evaluated in this study [62].

In a recently published study, a RCT was performed to assess the efficacy of EMS in preventing CIPNM. A total of 140 critically ill patients were randomly assigned to an EMS group (n = 68) or to a control group (n = 72) after 24-48 hours of admission. Patients in the treatment group daily received 55 minutes EMS sessions of both lower extremities for as long as they were treated in the ICU. A diagnosis of CIPNM was made by use of MRC. Of the 140 critically ill patients, 52 patients could finally be evaluated. CIPNM was diagnosed in three patients in the EMS group and in 11 patients in the control group (OR = 0.22, p = 0.04). The MRC score was significantly higher in the EMS group than in the control group (58 versus 52, p = 0.04), and the ICU stay was shorter in the EMS group than in the control group (14 versus 22 days). Those patients who developed CIPNM had a prolonged long-term weaning period, 12 days versus one day (p = 0.0001), and a longer ICU stay, 25 versus 11 days (p = 0.01). This RCT suggests that EMS sessions can prevent the development of CIPNM in critically ill patients. EMS treatment also results in a shorter duration of MV and a shorter ICU stay in patients who do not develop CIPNM. EMS was well tolerated and resulted in an improvement of muscle performance, such as maximum voluntary contraction, and no side effects occurred during the EMS sessions. Furthermore, EMS did not require the cooperation of the patients and can be applied to any muscle group immediately upon ICU admission [21].

Prognosis

CIPNM significantly increases the length of MV and the lengths of ICU and hospital stays [57, 63]. In patients with CIPNM and MV for more than seven to ten days, the mortality increases from 19-56.5% to 48-84% [16]. A one-year follow-up study with 18 patients showed that all patients with CIM recovered fully, whereas only one of four with CIP recovered [64]. A five-year follow-up study with 47 critically ill, long-stay patients (> 28 ICU days) showed that > 90% had evidence of chronic partial denervation consistent with previous CIP after discharge (on average 43 months). Evidence of CIM was unusual [37]. This suggests that especially patients with CIP have long-term sequelae after discharge from the ICU.

DISCUSSION

One of the aims of this review was to determine whether new prevention/treatment modalities of CIPNM have occurred over the past five years. Only five articles met our inclusion criteria, and only one of those was a RCT [21]. There are presently four methods to prevent/treat CIPNM: physiotherapy and training, minimal sedation, IIT and EMS.

Early physical training (starting from < 48 hours on MV) may create barriers and safety concerns. It has, however, been shown to be feasible and safe [20, 52,

! TEXT BOX

Critical illness myopathy and/or critical illness neuropathy are frequent and serious complications to intensive care that:

- delay weaning from mechanical ventilation
- increase the length of stay at the intensive care unit
- compromise rehabilitation and may result in a lifelong loss of function and in a reduction in quality of life.

It seems reasonable to ensure maximal functional status for survivors of intensive care unit stays by applying a multimodal therapeutic approach including:

- screening and early diagnosis is possible
- intensive insulin therapy
- minimal sedation
- early physiotherapy
- electrical muscle stimulation.

53, 65]. Early activities are facilitated by changes in culture, knowledge and experience with increased physiotherapy and training. The clinicians are required to reorganize and manage current practices that have the potential to interfere with mobility, create a strategy to improve the level of teamwork and link effective practice intervention and teamwork with short- and long-term patient-centred outcomes [66]. Early activity in the ICU can be limited for various reasons, but if ambulation becomes a priority, the probability of ambulation increases.

Although physiotherapy may not treat the course of CIPNM, it has repeatedly been shown to be highly beneficial in critically ill patients. Physiotherapy can be initiated with PROM when the patient is sedated. Physiotherapy is best performed by a team that includes a physiotherapist and in accordance with a protocol. Occupational therapy has also been used with good results. Physiotherapy, including the salary of the mobility team, does not increase expenses owing to the reduction in length of stay.

If the length of sedation is shortened and daily interruption of sedation with SBP is performed, the reduced sedation not only facilitates the possibility for active training, it has also been shown to reduce MV time, ICU stay and hospital stay in critically ill patients.

Strong evidence suggests that IIT is associated with a reduction in the number of ICU patients developing CIPNM [42].

EMS has shown to be well tolerated and may be initiated even when the patient is sedated. EMS has also been shown to be highly beneficial and to reduce CIPNM. However, as opposed to physiotherapy, the number of studies is limited, especially as regards studies combining EMS and physiotherapy.

This review is limited by the relatively small amount of studies, especially in regard to EMS. Some articles have focused on special patient groups, e.g. patients with CHF, COPD, acute respiratory distress syndrome (ARDS) or a selected type of ICU, which makes it difficult to generalize the results. Most authors agree that CIPNM is a serious complication. There is evidence showing that CIPNM may result in lifelong loss of function and decreased quality of life. However, also survivors from ARDS have persistent functional disability, mainly muscle wasting and weakness one year after discharge from ICU even without CIPNM [67].

CONCLUSION

CIPNM is the most commonly occurring ICU-acquired neuromuscular dysfunction, and it is associated with a significant increase in length of stay, delayed weaning from MV, prolonged rehabilitation and, consequently, more expenses. To treat/prevent this condition, it seems reasonable to ensure maximal functional status for survivors of ICU-stay by applying a multimodal therapeutic approach including IIT, minimal sedation and – as suggested by new evidence – early physiotherapy and EMS.

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CONFLICTS OF INTEREST: none

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