

# Update in Nonpulmonary Critical Care

## Acquired Neuromuscular Disorders in the Intensive Care Unit

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Neuromuscular abnormalities developing as a consequence of critical illness can be found in the majority of patients hospitalized in the intensive care unit (ICU) for 1 week or more (1–3). The spectrum of illness ranges from isolated nerve entrapment with focal pain or weakness, to disuse muscle atrophy with mild weakness, to severe myopathy or neuropathy with associated severe, prolonged weakness. This update focuses on disorders associated with diffuse, severe weakness.

The prevalence and impact of acquired neuromuscular weakness is likely larger than generally recognized. Greater than 50% of patients mechanically ventilated for more than 7 days will develop electrophysiologic abnormalities (4), with 25–33% developing clinically overt weakness (5, 6). Acquired neuromuscular dysfunction is associated with difficulty in separating from mechanical ventilation, increased hospital costs, and increased mortality (3, 7). The potential economic impact of this problem is large, with one estimate of an average of \$66,000.00 per patient in excess hospital charges attributable to acquired neuromuscular weakness in the ICU (1996 U.S. dollars) (8).

A clear classification of ICU-acquired neuromuscular disorders is difficult because of inconsistencies in reporting, testing, and terminology in the existing literature. For example, just some of the terms describing weakness syndromes in the ICU and the associated acronyms include critical illness polyneuropathy (CIP or CIPN), neuromuscular disorders (NMDs), acute quadriplegic myopathy (AQM), critical illness neuromuscular abnormalities (CINMAs), and ICU-acquired paresis (ICUAP). To complicate matters further, studies suggest that patients diagnosed with critical illness polyneuropathy (CIPN) may in fact have myopathy as a contributing if not primary cause of weakness. This has led to the coining of an additional term, critical illness polyneuropathy and myopathy (CIPNM), which reflects the difficulty discriminating between myopathic and neuropathic causes of weakness syndromes acquired in the ICU. Last, although the so-called acute quadriplegic myopathy (AQM) first described in patients with severe acute asthma and other types of respiratory failure has often been described as a distinct entity, there is overlap between AQM and CIPNM.

Given the above caveats, this update focuses on three causes of severe, diffuse weakness in the ICU: prolonged neuromuscular blockade, CIPNM, and AQM, and discusses the shared and unique features of these disorders. Our goal is to increase aware-

ness of the frequency, severity, and potential for long-term morbidity of ICU-acquired weakness, to provide critical care clinicians a framework for understanding the etiology, prevention, diagnosis, and treatment of ICU-acquired weakness, and to stimulate the development of research in this important area. In addition, we present a general algorithm for approaching unexplained weakness in patients recovering from critical illness in the context of this framework (Figure 1).

### PROLONGED NEUROMUSCULAR BLOCKADE

#### Etiology

“Nondepolarizing” neuromuscular blocking drugs (NMBDs) are competitive inhibitors of neuromuscular transmission, and are either benzylisoquinolinium (atracurium, cisatracurium, and doxacurium) or aminosteroid (pancuronium, vecuronium, pipecuronium, and rocuronium) in structure. Most of the pharmacokinetic and dynamic data on these agents is drawn from short-term intraoperative administration to facilitate surgery and that experience may not predict the effect of these drugs in the dynamic ICU milieu. NMBDs are sometimes administered to critically ill patients in conjunction with sedation in an effort to facilitate mechanical ventilation, reduce oxygen consumption, and control intracranial pressure. There is no evidence demonstrating improved outcomes with the use of NMBDs in the ICU, and preliminary evidence suggests that NMBDs may have a negative impact on mortality and ICU length of stay (9). Clearly, the potential for both short- and long-term complications due to their use is large. Nonetheless, they remain important agents for judicious use in the ICU setting.

Most of the NMBDs rely to various degrees on a combination of hepatic metabolism and renal elimination for termination of effect. Thus, large doses of NMBDs in the setting of renal failure can result in prolonged neuromuscular blockade after only a few hours of administration. Moreover, the products of hepatic metabolism of pancuronium and vecuronium have 50–60% of the potency of the parent compounds and are renally cleared (10). The use of pancuronium and vecuronium in the presence of renal failure has resulted in neuromuscular blockade for days and even weeks after discontinuation of drug administration (11, 12).

Atracurium and cisatracurium are novel NMBDs in that they are metabolized in plasma by ester hydrolysis and Hoffman degradation, and require neither the liver nor kidney for metabolism and elimination. Although more expensive than vecuronium or pancuronium, atracurium or cisatracurium are preferred agents in the setting of renal and/or hepatic failure because of their predictable duration of action (13).

Additional risk factors for prolonged neuromuscular blockade include hypermagnesemia, metabolic acidosis, female sex (11), and the concomitant use of various antibiotics, including aminoglycosides and clindamycin. However, none of these factors is likely to be as important as renal failure.

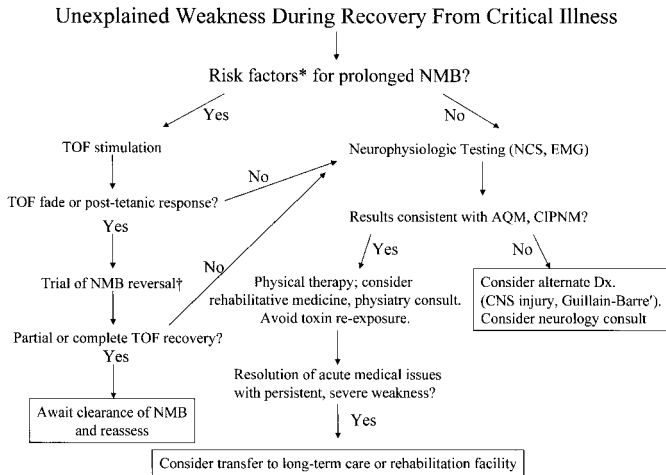
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**Figure 1.** Algorithm for evaluating unexplained weakness during recovery from critical illness. AQM = acute quadriplegic myopathy; CIPNM = critical illness polyneuropathy and myopathy; CNS = central nervous system; Dx = diagnosis; EMG = electromyogram; NMB = neuromuscular blockade; TOF = train of four. \*Risk factors for prolonged NMB: repeated or prolonged administration of medium-long duration NMB drug combined with renal and/or hepatic failure. For example, neostigmine 0.05 mg · kg<sup>-1</sup> plus glycopyrrolate 0.01 mg · kg<sup>-1</sup> (to counteract muscarinic effects of excess acetylcholine).

## Prevention

Prolonged neuromuscular blockade is best avoided by limiting the dose and duration of NMBD administration, particularly in high-risk settings such as renal or hepatic failure, and by frequently monitoring the drug effect (13). The best way to monitor drug effect in the ICU is not clear. Peripheral nerve stimulation with measurement of the response to four equal pulses over 2 seconds (train of four, or TOF) is the “gold standard” for monitoring neuromuscular blockade in the operating room. Although TOF monitoring may result in the use of lower doses of NMBDs and faster recovery from neuromuscular blockade in patients in the ICU (14), clinical evaluation may be just as effective (15). Frequent scheduled drug “holidays” with clear evidence of recovery from neuromuscular blockade (patient movement) may be the best insurance against prolonged neuromuscular blockade in the ICU, and will also guarantee that the paralyzed patient is adequately sedated.

## Diagnosis and Treatment

The diagnosis of prolonged neuromuscular blockade is made by documentation of lack of or attenuated response to TOF stimulation. Treatment consists primarily of waiting for clearance of NMBD. Pharmacologic reversal of neuromuscular blockade with a cholinesterase inhibitor may also be useful in establishing a diagnosis (Figure 1), but recovery will likely be incomplete or short-lived in the presence of high concentrations of NMBDs or their metabolites.

## CRITICAL ILLNESS POLYNEUROPATHY AND MYOPATHY

### Incidence and Etiology

Prospective studies show that 25–36% of patients receiving intensive care are weak by clinical evaluation (5, 6). However, clinical evaluation underestimates the true incidence of nerve and muscle dysfunction in ICU patients (5, 16). Prospective studies using neurophysiologic testing reveal that neuropathy

and/or myopathy is present in 52–57% of patients in the ICU for 7 days or more (4, 17), and in 68–100% of patients with sepsis or systemic inflammatory response syndrome (SIRS) (3, 18, 19). Prospective studies that include muscle biopsy confirm that myopathy is common among ICU patients, demonstrating an incidence from 48 to 96% (2, 20).

Despite the high incidence of CIPNM, clinical risk factors are still unclear. Multiple potential risk factors have been investigated in a number of prospective studies, yielding contradictory results. These studies are limited by small numbers; however, inconsistent eligibility criteria and varying case definitions prevent combining the results by metaanalysis (21). Nonetheless, using information gained from these studies and laboratory investigations, a few preliminary conclusions can be drawn.

Sepsis and multiorgan dysfunction increase the risk of CIPNM, as shown in both retrospective and prospective series (4, 6, 18–20, 22, 23). In one small prospective series, electrophysiologic evidence of acute neuropathy was present as early as 2 days after the diagnosis of sepsis (18). Thus, CIPNM likely represents an organ failure of sepsis and SIRS, presumably as a result of the same basic mechanisms that lead to multiple organ dysfunction, such as inflammation, apoptosis, thrombosis, and oxidant injury. Unfortunately, there is limited experimental evidence supporting the roles of these mechanisms in sepsis-related neuropathy and myopathy.

There is only one published randomized, controlled trial designed with CIPNM as an outcome measure (17). In this study of the effect of an intensive insulin protocol on ICU morbidity and mortality, tight glycemic control achieved via the protocol led to a decrease in CIPNM. Among 363 subjects requiring seven or more days of intensive care, the rate of CIPNM defined by neurophysiologic testing was reduced from 51.9% among control subjects to 28.7% among subjects treated with the intensive insulin protocol. Hyperglycemia has been associated with an increased risk of CIPNM in multiple studies (6, 16, 24). The link between hyperglycemia and CIPNM may be related to a combination of the toxic effects of hyperglycemia and the anti-inflammatory and neuroprotective effects of administered insulin that have been demonstrated experimentally (25, 26).

Other disease-specific factors shown to be associated with CIPNM in multiple studies include severity of illness (3, 5) and duration of ICU stay (6, 16, 27). Patient-specific factors may also increase the risk of CIPNM, including female sex (6) and increased age (3).

Factors associated with the treatment and complications of critical illness may also increase the risk of CIPNM. Treatment with corticosteroids or neuromuscular blocking agents may also be associated with development of CIPNM. Although these associations have been demonstrated only in relatively small observational studies (3, 6), experimental evidence supports the role of both corticosteroids and neuromuscular blocking agents in the development of acute myopathy, in particular. Observational studies have identified possible additional risk factors such as aminoglycoside antibiotics (4), catecholamines/vasopressors (17, 28), parenteral nutrition (3), and renal replacement therapy (17). However, these potential risk factors are all integrally related to sepsis and severity of illness; their causal relationship to CIPNM is unclear.

The spectrum of pathology in CIPNM includes pure neuropathic changes, pure myopathic changes, and combined neuropathic and myopathic changes. The relative distribution of neural versus muscle involvement in CIPNM has been difficult to define, in part because of inconsistencies in testing and interpretation of basic neurophysiologic studies: nerve conduction studies and electromyography (EMG). Results from these tests can be relatively nonspecific and may not allow differentiation between

nerve, neuromuscular junction, and muscle abnormalities (29), and most studies do not include muscle biopsy. Although earlier reports emphasized the predominance of neuropathy in weakness associated with critical illness (4, 30), work using more sensitive techniques for the detection of myopathy has found that the majority of patients with CIPNM have evidence of nonneuropathic myopathy (29). In addition, a report of patients with neurophysiologic evidence of CIP found only myopathy on muscle biopsy, with normal nerve morphology (31). Thus, it is becoming increasingly clear that neuropathy may play a far less important role than once thought in ICU-acquired weakness.

### Prevention

As described earlier in the text, intensive insulin therapy has been shown to reduce the risk of CIPNM, leading to a dramatic reduction in the risk of developing CIPNM compared with control subjects (odds ratio, 0.4; 95% confidence interval, 0.28–0.57;  $p < 0.0001$ ) (personal communication, G. van den Bergh). In addition, mean blood glucose level has been shown to be an independent risk factor for CIPNM, as described in the follow-up study, which analyzed data from all patients in the intervention and control groups of the original study ( $n = 1,548$ ) (24). These data suggest that a relatively simple and inexpensive intervention in the ICU may have significant long-term benefits in recovery from critical illness in addition to the shorter term mortality benefits shown (17).

Efforts to prevent and aggressively treat sepsis will likely reduce the incidence of CIPNM. Beyond this obvious strategy, it is unclear whether specific therapies directed at the inflammatory cascade of sepsis will reduce the incidence of CIPNM. If duration of intensive care is associated with CIPNM, measures that reduce ICU length of stay may also decrease CIPNM. These measures include prevention of ventilator-associated pneumonia through use of semirecumbent positioning, reduction of ventilator-induced lung injury in patients with acute lung injury through use of low tidal volume mechanical ventilation, and limitation of sedative infusions through protocols that provide daily interruptions of sedative infusions.

### Diagnosis and Treatment

Diagnostic testing (nerve conduction studies/electromyography) should be considered in patients with unexplained weakness during or after recovery from critical illness (Figure 1). An established diagnosis of CIPNM may be helpful in determining disposition, as early transfer to long-term care or rehabilitative facilities may be appropriate in some cases. Diagnostic testing may also reveal the presence of other, potentially treatable neuromuscular disorders (e.g., prolonged neuromuscular blockade or Guillain-Barré syndrome), obviate an extensive search for alternative etiologies of weakness, and highlight the importance of avoiding potential neurotoxic/myotoxic agents in patients with established CIPNM. At this point in time, no treatments for established CIPNM have been proven to be effective.

## ACUTE QUADRAPLEGIC MYOPATHY

### Etiology

The development of acute myopathy during treatment of severe acute asthma was initially described in 1977, with sporadic case reports over the ensuing decade (32). In part because of the association between chronic corticosteroid use and myopathy, initial reports of acute myopathy in individuals with asthma focused on the role of corticosteroids (33). It became clear in the 1990s that the use of prolonged neuromuscular blockade was also associated with the development of acute myopathy (34, 35). Although the type and dose of corticosteroid do not

appear to be risk factors for the development of myopathy (27), increasing duration of neuromuscular blockade does appear to be a risk factor (35).

Because vecuronium and pancuronium contain an aminosteroid nucleus, it was hypothesized that these specific agents might have an additive toxic effect with corticosteroids on muscle (34). However, multiple reports of myopathy developing after the use of structurally unrelated NMBDs (atracurium, cisatracurium, and doxacurium) have since surfaced (36, 37), suggesting that the earlier reports were related to the frequency of administration of the drugs rather than a specific steroid effect. Likewise, there are some reports of patients with acute respiratory failure developing acute myopathy in the absence of corticosteroids, neuromuscular blockade, or both (38). Thus, although corticosteroids and NMBDs appear to be risk factors for the development of acute myopathy, other unidentified factors are also important. There is likely overlap between this syndrome and CIPNM.

The development of acute AQM is not unique to asthma, as the syndrome has been reported in association with respiratory failure of various causes, including the acute respiratory distress syndrome; sepsis; and after heart, lung, and liver transplantation (38). The unifying factors in most cases are the administration of corticosteroids and/or NMBDs in the setting of acute respiratory failure.

Electromyography reveals reduced muscle membrane excitability in patients with AQM (29, 39, 40). Muscle pathology appears to take at least two forms, although it is possible that they represent a spectrum of the same injury. One major variant appears as selective thick (myosin) filament loss and the second as widespread myonecrosis (38). The latter may explain reports of rhabdomyolysis in association with status asthmaticus (33). The simultaneous presence of both thick filament loss and rare necrosis in some cases suggests there may be a spectrum of injury between the two variants. Furthermore, the risk factors for each variant of myopathy and the clinical courses do not appear to differ. Both of these forms are clearly distinguishable from the myopathy associated with chronic corticosteroid use, which appears as Type II fiber atrophy on muscle biopsy.

The pathogenesis of AQM is not clear. The direct toxicity of NMBDs has not been established and it is possible that these agents play a potentiating role, by virtue of pharmacological “denervation,” that facilitates the toxic effects of other agents such as corticosteroids or inflammatory mediators. In addition, the functional denervation resulting from nerve injury in CIPNM may provide a link between CIPNM and AQM. In animal studies, denervation results in proliferation of steroid receptors on muscle membrane and subsequent steroid administration results in muscle thick filament loss and loss of membrane excitability (41), providing some support to the potentiating role of NMBDs or acquired polyneuropathy in the development of AQM. However, the mechanism for development of AQM remains elusive, largely because of the paucity of animal data and inconsistent testing and reporting in clinical series.

### Prevention

The risk of acute myopathy in association with corticosteroid and NMBD administration appears to increase after 24–48 hours of therapy (35, 42). The use of these agents should be limited to as short a time course as possible and clinicians should reassess the indication for these drugs on a daily basis. Deep sedation may often substitute for neuromuscular blockade, although deep sedation with immobility may also pose some risk for the development of AQM. However, at least two studies have found no relationship between ICU-acquired weakness and the total dose of administered sedative (5, 6), suggesting that deep sedation may be a safer alternative than neuromuscular blockade.

## Diagnosis and Treatment

The diagnosis of AQM should be suspected in the presence of unexplained quadriplegia in ICU patients with a history of corticosteroid or NMBD use. Weakness of AQM affects both proximal and distal muscles, including the diaphragm, and can be profound. Reflexes may be present or absent, but sensation remains intact. Serum creatine phosphokinase levels may be normal or elevated during the acute phase of myopathy and significant elevations may identify patients at risk of rhabdomyolysis. Neurophysiologic testing can support the diagnosis of acute myopathy and help rule out other causes of neuromuscular weakness (Figure 1). Although muscle biopsy may provide a definitive diagnosis, it is not clear that this invasive procedure adds sufficient information to warrant its routine clinical use.

There is currently no specific therapy defined for AQM. Reexposure to corticosteroids and/or NMBDs should be avoided, as relapse of myopathy has been reported after recovery from an initial incident followed by reexposure to high-dose corticosteroids (33). In some patients, recovery from myopathy can be rapid and occur over days to weeks, whereas in others recovery takes months to years and necessitates prolonged mechanical ventilation and rehabilitative therapy.

## EFFECT OF ICU-ACQUIRED NEUROMUSCULAR WEAKNESS ON PATIENT OUTCOMES

There is some evidence of the effect of ICU-acquired neuromuscular weakness on patient outcomes; most of these data pertain to CIPNM. Patients with CIPNM have an increased risk of death. A prospective study suggested that CIPNM independently increased the odds of in-hospital death sevenfold, although excluding residual confounding by severity of illness is difficult in such studies (3). Amongst survivors, CIPNM is associated with prolonged mechanical ventilation, hospitalization, and rehabilitation (3, 4, 28). Although complete recovery from CIPNM can occur in weeks, many patients with severe CIPNM will have persistent deficits and diminished quality of life after 1 year of follow-up (43). In one prospective study, 16 of 17 patients with clinical weakness and evidence of CIPNM during ICU stay had persistent mild weakness 9 months later (6). More ominously, de Sèze and coworkers found that 6 of 19 patients (31%) with severe CIPNM had persistent tetraplegia at 2 years of follow-up (44). A follow-up study of 22 nonconsecutive survivors of prolonged critical illness with quadriplegia demonstrated clinical examination findings of sensory deficits in 6 of 22 patients and weakness in 4 of 22 patients 1 year or more after ICU discharge (45). Twenty of the 22 patients had neurophysiologic evidence of chronic partial denervation, and 7 still required significant assistance in performing activities of daily living. Because this study included only patients who were well enough to travel and participate in testing, it is likely that morbidity is underestimated.

Survivors of critical illness have sustained impairments in physical function and health status even after 1 year of recovery (46, 47). In a 1-year follow-up study of 109 survivors of adult respiratory distress syndrome (ARDS), Herridge and coworkers found that all subjects reported a limited functional status attributed to muscle weakness and fatigue (48). Despite normalized pulmonary function, survivors continued to have impairments of health-related quality of life and exercise tolerance. The etiology of the weakness is unknown, but the risk factors are the same as for CIPNM. It is likely that ICU-acquired neuromuscular disorders play an important role in the prolonged disability of survivors of critical illness.

## FUTURE RESEARCH

It has been more than 100 years since Osler described the development of tetraplegia in a patient with sepsis (49), yet research on the neuromuscular sequelae of critical illness remains in the early stages. Better animal models and improved epidemiologic studies of incidence and risk factors with complete evaluation of all ICU patients at risk are needed. Systematic follow-up studies of ICU survivors and the inclusion of neuromuscular function as an outcome measure in ICU interventional trials should be encouraged. Finally, interventional studies evaluating prevention and treatment of neuromuscular dysfunction in the ICU and after discharge must be pursued. Such research will promote understanding of the pathophysiology and allow development of strategies to protect patients from and treat patients with neuromuscular sequelae of critical illness.

## Conclusions

Neuromuscular weakness that is acquired as a result of critical illness and/or therapy is more common than recognized and may result in substantial excess morbidity, mortality, and costs. Understanding of ICU-acquired paresis remains incomplete and recognition of its importance has implications for clinical practice and future research. Neuromuscular dysfunction may be reduced by avoiding neuromuscular blocking agents, limiting corticosteroids to patients with clear indications, treating hyperglycemia with intensive insulin therapy, and providing ICU supportive care that limits end-organ dysfunction, such as low tidal volume ventilation for patients with ARDS. All ICU patients should be clinically screened for weakness to help plan treatment, avoid potential toxin reexposure, and identify patients for rehabilitative treatments. Clinicians who care for survivors of critical illness need to understand and address the effect of persistent neuromuscular dysfunction on their patients' health status.

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