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Review

Approach to Neuromuscular Disorders in the Intensive Care Unit

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Abstract

Neuromuscular disorders increasingly are recognized as a complication in patients in the intensive care unit (ICU) and represent a common cause of prolonged ventilator dependency. The distinct syndromes of critical illness myopathy, prolonged neuromuscular blockade, and critical illness polyneuropathy (CIP) may arise as a consequence of sepsis, multi-organ failure, and exposure to various medications—notably, intravenous corticosteroids and neuromuscular blocking agents—but the pathophysiology of these disorders remains poorly understood. More than one syndrome may occur simultaneously, and the distinctions may be difficult in a particular patient, but a specific diagnosis usually can be established after careful clinical, electrodiagnostic, and, when necessary, histological evaluation. For example, asthmatics requiring treatment with corticosteroids and neuromuscular blocking agents may develop an acute myopathy characterized by generalized weakness, preserved eye movements, elevated creatine kinase levels, and myopathic motor units on electromyography (EMG). Muscle biopsy demonstrates distinctive features of thick (myosin) filament loss on ultrastructural studies. Conversely, those with a prolonged ICU course that is complicated by episodes of sepsis with failure to wean from the ventilator, distal or generalized flaccid limb weakness, and areflexia probably have CIP. EMG in these patients demonstrates reduced or absent motor and sensory potentials with neurogenic motor units. Prolonged neuromuscular blockade most commonly occurs in patients with renal failure who have received prolonged infusions of neuromuscular blockers. There is severe flaccid, areflexic paralysis with normal sensation, facial weakness, and ophthalmoparesis that persists for days or weeks after the neuromuscular blockers have been discontinued. Repetitive nerve stimulation shows a decrement of the compound muscle action potential and, in most cases, establishes a disorder of neuromuscular transmission. With the recent epidemic of West Nile virus infection, a clinical syndrome of acute flaccid paralysis with several features indistinguishable from poliomyelitis has emerged. This article critically examines the clinical, electrophysiological, and pathological features of these and other acute neuromuscular syndromes that arise in the context of ICU care and summarizes the current understanding of the pathophysiology and treatment of these disorders.

Key Words: Critical illness myopathy; critical illness polyneuropathy; prolonged neuromuscular blockade; West Nile virus; acute flaccid paralysis; weakness; paralysis; intensive care unit.

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Introduction

Generalized weakness in critically ill patients is a frequent complication in an intensive care unit (ICU) and is a common cause of prolonged ventilator dependency *(1)*. Intravenous corticosteroids and neuromuscular blocking agents, sepsis, and multi-organ failure have been strongly implicated in the ICU-paralysis syndromes, but the pathophysiology of these disorders is not

Table 1
Approach to Evaluation of the Patient With Weakness in the ICU

Weakness before ICU admission	*Weakness after ICU admission*
Spinal cord disorders	
Ischemic myelopathy	
Acute epidural compression resulting from infection or neoplasm	
Acute transverse myelitis	
Acute ischemia	
Traumatic myelopathy	
Motor neuron disease	
Amyotrophic lateral sclerosis variants	Acute flaccid paralysis–West Nile virus infection
Poliomyelitis (nonpoliovirus, West Nile virus)	
Acute neuropathies	Critical illness polyneuropathy
GBS and variants	
Porphyria	
Carcinomatous meningitis	
CMV polyradiculopathy (HIV infection)	
Acute vasculitis neuropathy	
Chronic neuropathies	
Chronic inflammatory demyelinating polyneuropathy and variants	
Neuromuscular Junction Disorders	
Myasthenia gravis	Prolonged neuromuscular blockade
Lambert–Eaton syndrome	
Botulism	
Tick paralysis	
Organophosphate poisoning	
Myopathies	
Rhabdomyolysis	Critical illness myopathy
Polymyositis	Pyomyositis
Muscular dystrophy	
Mitochondrial myopathy	
Acid Maltase deficiency	
Acute alcoholic myopathy	
HIV myopathy	
Sarcoid myopathy	
Acute viral myositis	
Miscellaneous	
Hypocalcemia	
Hypomagnesemia	

CMV, cytomegalovirus; GBS, Guillain–Barré syndrome; HIV, human immunodeficiency virus.

completely understood *(1–34)*. In addition to the neuromuscular illnesses that often require ICU management (e.g., Guillain–Barré syndrome [GBS], myasthenia gravis, acute flaccid paralysis as a complication of West Nile virus), this article emphasizes several distinct neuromuscular syndromes that may arise *de novo* in patients in the ICU—specifically, critical illness myopathy (CIM, also termed acute steroid myopathy or acute quadriplegic myopathy), prolonged neuromuscular blockade, and critical illness polyneuropathy (CIP). Although several useful reviews of these conditions have recently appeared, they give the impression that the etiologies of these syndromes are well understood and that the processes are mutually exclusive *(22–34)*. Many accepted cases in the literature uncritically add to these notions. More than one syndrome may occur simultaneously, and the distinctions may be difficult in a particular patient, but a specific diagnosis usually can be established after careful clinical, laboratory, electrodiagnostic, and histopathological evaluation *(35)*. It is useful for clinicians to consider neurological disorders that cause paralysis prior to ICU admission, in contrast to weakness that develops in established patients in the ICU (Table 1).

Disorders of Muscles

Critical Illness Myopathy

Critical care physicians and anesthesiologists have long recognized a syndrome of severe generalized weakness associated with corticosteroids and neuromuscular blockers (NMBs) that has subsequently been attributed to an acute myopathy. In 1977, MacFarlane and Rosenthal *(36)* first reported this illness in a 24-year-old asthmatic who became quadriplegic after treatment with large doses of hydrocortisone (3 g in 24 hours) and pancuronium. There have been at least 60 additional reviews detailing the clinical features of more than 200 similar patients *(3–8,17,18,37–73)* with a condition variously described as acute hydrocortisone myopathy *(36,37)*, acute quadriplegic myopathy *(4)*, necrotizing myopathy *(5,6,42)*, thick filament myopathy *(44,45)*, postparalysis syndrome *(7)*, acute myopathy of intensive care *(71)*, and CIM *(1,29,30,65)*. Many reports have considered this myopathy to be an acute effect of corticosteroids alone *(4,37,45,57,74)*, but evidence suggests that NMBs and possibly other factors (e.g., sepsis, trauma, other medications) have a significant role; because of this ambiguity, the term CIM seems preferable until the origins and limits are better elucidated *(30,75)*. The majority of patients with CIM have an exacerbation of acute asthma or emphysema, requiring treatment with high-dose intravenous steroids and mechanical ventilation, and the disorder also has been described in patients with severe acute respiratory distress syndrome *(76)*. All but a handful of reported cases also received NMB *(4,37,45,57,74)*.

Patients with CIM who are in the ICU have persistent, moderate or severe, flaccid generalized weakness that becomes apparent after the NMBs have been discontinued (Table 2). Unlike most myopathies (which have a predilection for proximal muscles), distal and proximal muscles may be affected equally, and distal weakness occasionally predominates *(50)*. Limb tone is reduced, and over time, the muscles become atrophic. The weakness is usually symmetric but, rarely, may begin in one limb. The reflexes may be normal, reduced, or absent, the latter being atypical for most myopathies.

Preserved sensation usually helps to differentiate myopathy from CIP (which will be discussed later), but both can occur simultaneously and confound the clinical evaluation *(1,13,77,78)*. Ophthalmoparesis, ptosis, and facial weakness have been reported in at least five patients and can lead to diagnostic confusion by suggesting the presence of prolonged neuromuscular blockade; more recent studies have suggested that facial weakness may be present in more than half of patients *(7,40,51,66,71)*. The most prominent ICU problem is the delay in weaning caused by diaphragmatic or intercostal

Table 2
Features of Critical Illness Myopathy

Moderate-to-severe generalized weakness proximal muscles, proximal and distal, rarely distal predominant symmetric
Reduced limb tone
Muscle atrophy (may be absent early on)
Normal or reduced reflexes may be absent in severely affected muscles
Cranial nerves usually spared
Rarely, ophthalmoparesis, facial weakness
No ptosis
Sensation normal (may be difficult to assess)
Ventilatory (not respiratory) failure
Failure to wean (often reason for consultation)
Reduced vital capacity, tidal volume, negative inspiratory force
CK may be elevated or normal
EMG: low motor amplitudes, normal sensory potentials, myopathic motor units
Cerebrospinal fluid is normal
Muscle biopsy: acute muscle fiber degeneration, no inflammation, abnormal myosin ATPase activity, thick filament loss on electron microscopy

CK, creatine kinase; EMG, electromyography; ATP, adenosine triphosphate.

muscle weakness, and in a few patients, ventilatory failure is the presenting symptom *(3,34,35)*. Most patients recover after 4 to 12 weeks, but 14 reported patients remained weak for 4 months or more *(4,37–40,44,50,60,61,73)*. Rarely, recovery is incomplete, and at least 19 patients have died from medical complications *(5–7,44,49,73)*. CIM has been reported in children and infants, and the syndrome is virtually identical to what has been described in adults *(39–40,52)*.

Laboratory evaluation fails to demonstrate other causes for acute generalized weakness, such as hypokalemia, hypophosphatemia, or hypermagnesemia. Although the serum creatine kinase (CK) concentration usually is increased at least three times above normal and frequently may be 100-fold higher or more *(53)*, at least 15% of patients in well-documented cases have normal CK levels throughout hospitalization. In a prospective study, the CK peak occurred an average of 3.6 days after exposure to steroids or NMBs, and the levels remained elevated for approximately 10 days, indicating that increased CK values may be missed if measured later in the illness *(53)*. When the CK is markedly elevated, there may be myoglobinuria and renal failure.

Electrophysiological studies are useful in establishing the myopathic nature of this disorder. Compound muscle action potentials (CMAP) are low in amplitude in the affected limbs, but the CMAP may be near normal if weakness is mild. Conversely, greatly reduced CMAPs may also be observed in terminal motor axonal neuropathies, confounding the important distinction from CIP (*see* critical illness polyneuropathy) *(71)*. Unless patients have a concurrent polyneuropathy, the sensory nerve potentials are preserved, although sensory nerve studies may be limited by limb edema in critically ill patients or other technical factors related to performing electrodiagnostic studies in an ICU setting *(31–34,54)*. Therefore, the absence of the sensory nerve action potential does not exclude CIM *(79)*. Motor nerve conduction velocities and distal latencies usually are normal or near normal.

Direct muscle stimulation is a recently described technique that may be useful in differentiating CIP from CIM *(80,81)*. In patients with CIM, muscle is electrically inexcitable following direct stimulation, in contrast to denervated muscle, which has a normal electrical response to direct muscle stimulation, despite an absent or markedly reduced distal CMAP amplitude following nerve stimulation *(80,81)*. Therefore, the ratio of the CMAP amplitude evoked by nerve stimulation to that evoked by direct muscle stimulation is suggestive of myopathy when greater than 0.5 and is consistent with neuropathy when less than 0.5 *(80)*. This technique has subsequently been validated by Trojaborg and colleagues *(81)*, who found that the nerve CMAP to muscle CMAP ratio was greater than 0.5 in 13 patients with CIM in their ICU.

As expected, motor unit potentials are small, short in duration, polyphasic, and have normal or early recruitment, all of which are typical features of a myopathy. One study demonstrated that quantitative motor unit analysis showed the mean motor unit duration was less than 20% of controls and that motor unit number estimation was normal, both of which are consistent with myopathy *(81)*. These advanced techniques may distinguish myopathic from neurogenic motor units, but patients with severe weakness may be unable to recruit any motor units for analysis. Furthermore, when direct muscle stimulation is compared to muscle and nerve histopathology obtained by tissue biopsy, myopathic and neuropathic features frequently co-exist *(82)*.

The needle electromyography (EMG) examination shows variable amounts of abnormal spontaneous activity (fibrillation potentials) in weak muscles. In the case of CIM, these fibrillation potentials (usually an indication of nerve disease) are believed to reflect muscle fiber necrosis, which causes a functional disconnection of the motor end-plate from the muscle fiber membrane *(5,6,30)*. Such fibrillation potentials can be diagnostically useful because they are usually seen earlier (i.e., within days of the onset of weakness) in CIM than in neurogenic disorders such as CIP.

There is no decrement in the amplitude of the CMAP following repetitive nerve stimulation or twitch tension studies ("train-of-four" [TOF]). The exception occurs in a few patients in whom EMG studies performed soon after the onset of paralysis demonstrate residual neuromuscular blockade that is juxtaposed on the myopathy. In CIM, an improvement in CMAP amplitudes with serial testing parallels the clinical recovery of muscle power. Fibrillation potentials and myopathic motor units may persist for weeks or months, but follow-up studies are usually normal in patients who make a full recovery.

The combined nature of the defects found by the EMG in many patients with clinical features of CIM emphasizes the complexity of these cases and the difficulty in interpreting material in the literature *(82)*. For example, one prospective study indicated that 15 of 24 cases would have been misclassified as CIP if not for the muscle biopsy showing features of a myopathy *(77)*; in another series, 13 patients with a "sensorimotor polyneuropathy and motor syndrome" had direct muscle stimulation that demonstrated a myopathic pattern in 3 patients and a neuropathic pattern in 4 patients, whereas muscle biopsy demonstrated mixed neurogenic and myopathic

features in 3 patients, and nerve biopsy showed a sensory axonal neuropathy in 5 patients *(82)*.

CIM has been reported with methylprednisolone *(3–8)*, hydrocortisone *(36,37,39,41,62)*, prednisone *(7,46)*, betamethasone *(57)*, and dexamethasone *(38,53,57,60,70)*. Although a small study by Shee *(41)* suggested that myopathy was associated with the cumulative steroid dose, this has not been confirmed by others. The minimum dose and duration of steroid treatment required to produce CIM is difficult to estimate because of various confounding factors, including different routes of administration, intermittent treatment schedules, and different drug formulations and dosages in various studies (most published reports have not included the duration of steroid treatment). CIM has been reported after a treatment with dosages as low as 60 mg/day of prednisone for 5 days, although this must be rather uncommon *(7,74)*. When the dosage and duration of treatment has been well-documented, the majority of patients have received between 2 and 4 g of hydrocortisone or methylprednisolone for 1 to 4 weeks.

Similar difficulties have prevented accurate estimates of the minimum dose or duration of NMB treatment required to induce myopathy. Pancuronium and vecuronium are the drugs most often associated with CIM, but atracurium and other NMBs have been reported to cause a similar syndrome *(66–69,83)*. NMB dosages have ranged from a 10-mg single bolus to almost 8 g administered as a continuous infusion for 4 weeks; however, many of these cases have lacked adequate documentation of the clinical syndrome *(46)*. One biopsy-documented case of CIM occurred after only 164 mg of pancuronium was administered for less than 2 days, but most patients who have developed CIM have received between 500 and 4000 mg of a NMB *(50)*. Douglass and colleagues *(53)* found that patients with CIM received significantly greater amounts of vecuronium compared to asthmatic patients who did not develop myopathy. It is unknown whether there is any significance to the order in which these drugs are administered; NMB and corticosteroids are frequently administered concurrently, and most reports of CIM provide no details of the sequence of drug administration.

The relative contributions of NMB and corticosteroids to the development of CIM remain unsettled. For example, Barohn and coworkers *(7)* concluded that CIM is primarily related to steroids, not NMB; others have suggested an opposing view *(5)*. Adding to the confusion, numerous patients have been reported to recover after discontinuation of NMB when high-dose steroids were maintained or slowly tapered *(4,6)*. There have been several pathologically confirmed reports of CIM associated with steroids alone *(4,37,45,74,84)*; most showed characteristic myosin depletion, with or without scattered necrosis, and several had vacuolation and fiber regeneration, which is also characteristic of CIM *(74)*. At least 11 cases of CIM have been related to exposure to NMB without steroids *(49)*. Four others had myopathic biopsies, but no further details were provided *(59)*. Zochodne and associates *(5)* convincingly reported three patients with elevated CK levels and unequivocal myopathic EMG studies, but biopsies were not performed. Conversely, others have reported small series of patients with CIM associated with sepsis or multiorgan failure and without exposure to NMB or steroids *(76,85–87)*. The majority of experimental (*see* CIM Pathogenesis) and clinical evidence suggests that the combination of NMB and steroids is required to produce CIM in most cases, but occasionally, an identical syndrome occurs with either drug alone or as a consequence of other factors, including sepsis.

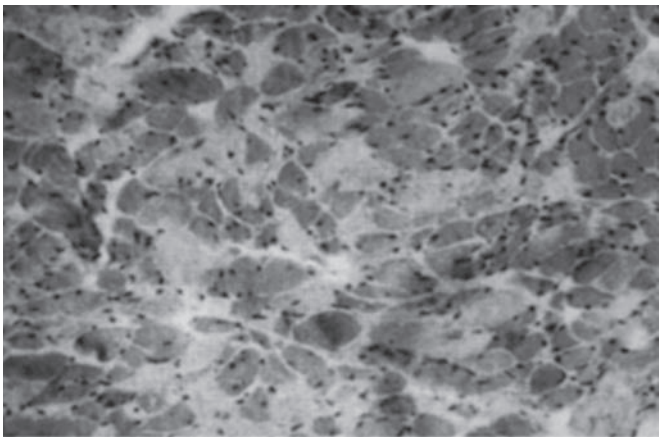

Fig. 1. Variation in fiber size and acute muscle fiber necrosis in a patient with critical illness myopathy.

Pathology

The histopathology of CIM is distinctive *(44,71)*. The muscle biopsy shows myopathic features, ranging from type II fiber atrophy to necrosis (refs. *6,71,72,87,88*; Figure 1). Frequently, there is atrophy of both fiber types. Muscle fiber necrosis is variable and ranges from mild scattered necrosis of isolated muscle fibers to severe widespread necrosis affecting all fiber types *(4,42,51,71)*. Inflammatory cells are absent, but a few studies have demonstrated class I major histocompatibility complex products and membrane attack complex expression on the surface membrane of some fibers, small perivascular inflammatory cell infiltrates, and expression of pro-inflammatory cytokines, implying a possible inflammatory component in some cases *(89–91)*. The adenosine triphosphate (ATP)ase stains often demonstrate extensive central pallor, with lack of staining of both fiber types *(4)*. The myofibrillar architecture often is disrupted with muscle fiber vacuolation. These vacuoles do not take up any of the usual histochemical stains and appear to represent expanded intermyofibrillar spaces when examined by electron microscopy *(6)*. There may be an increase in subsarcolemmal pools of glycogen or fat droplets *(4,40,46,74)*. Fetal myosin is increased in a proportion of myofibers, which is consistent with muscle fiber regeneration *(85)*.

Ultrastructural studies have demonstrated the most distinctive feature of CIM: a selective loss of thick (myosin) filaments (refs. *4,6–8,30,43–45,71,72*; Figure 2A,B). This is a prominent and consistent finding in CIM associated with exposure to corticosteroids and NMB or to corticosteroids alone *(45,71,72,79)*. Immunofluorescent studies have demonstrated that other muscle proteins (e.g., actin, troponin I) are maintained *(90)*. Others have shown an absence of myosin messenger RNA in pathological specimens during the acute illness with normal expression after recovery *(92)*. However, depletion of thick myosin filaments also occurs in several congenital myopathies, dermatomyositis, HIV infection, and other

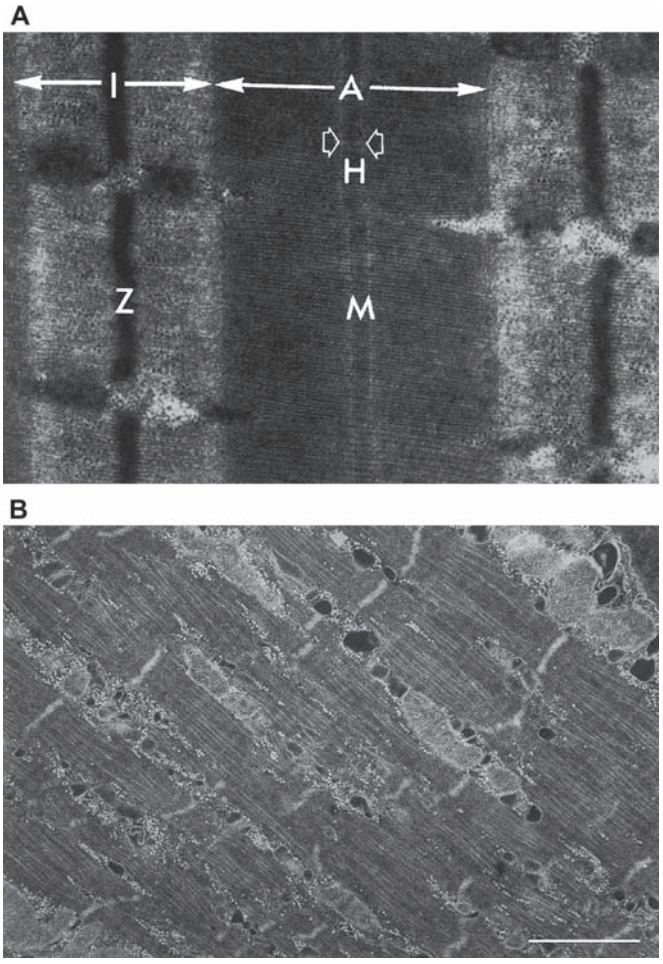

Fig. 2. **(A)** Electron microscopy of a normal muscle sarcomere. The thinner actin filaments are represented by the I-band, and the thicker myosin filaments are seen as the A-band. The darker M-line across the middle of the A-band represents the cross bridging of actin and myosin filaments. The lighter region in the mid-section of the A-band reflects the ends of the interdigitating actin filaments, referred to as the H-zone. The I-band is bisected by the Z-disc, where the actin filaments are inserted. **(B)** Electron microscopy of a muscle biopsy from a patient with critical illness myopathy. Note the widespread loss of myosin (thick) filaments.

disorders *(44,93,94)*. Al-Lozi et al. and others *(44,72)* reported thick filament loss in patients who developed a myopathy after lung or liver transplantation. Whether this disorder represents a variant of CIM remains to be established. Virtually all of the pathological specimens have been obtained from random needle or open muscle biopsy, and it is unknown whether thick filament depletion is a patchy or diffuse abnormality. Nonetheless, this distinct finding is useful to clinicians and justifies a muscle biopsy and electron microscopic examination when the diagnosis is uncertain. Sanders and coworkers *(79)* showed that many of their cases would have been misclassified as CIP based on clinical and EMG parameters; electron microscopy of muscle confirmed thick filament loss in all cases, and CIP was excluded by normal sural nerve biopsies.

Several patients have had a severe and near-total paralysis with flaccid areflexia, profuse fibrillation potentials, markedly elevated CK, myoglobinuria, and acute renal failure *(5,6,42,48)*. This has been attributed to diffuse muscle necrosis comparable to rhabdomyolysis, and muscle biopsy showed patchy myofiber necrosis in some patients. These patients received varying combinations of steroids and NMBs (particularly vecuronium in one study), and most also had multi-organ failure and sepsis *(5)*. Prolonged ventilator dependence and incomplete recovery was typical of patients in this group, and several died from sepsis or other medical complications *(5,6,42)*. Although Ramsay and coworkers *(6)* proposed that an "acute necrotic myopathy" in patients in the ICU might be distinguished by high CK levels, severe necrosis on muscle biopsy, and a worse prognosis, it is not certain whether the clinical, electrophysiological, and pathological features are sufficiently distinct to warrant differentiation from other cases of CIM.

Pathogenesis

Evidence suggests that CIM is a heterogeneous condition and that several different pathogenic pathways may converge to produce severe myopathy in patients in the ICU *(30,95)*. One explanation suggests that there is a direct myotoxic effect from the combination of steroids and NMBs. Dubois and Almon *(96)* observed an increase in the number of glucocorticoid receptors in the cytosol of denervated gastrocnemius muscle in rats. The enhanced expression of steroid receptors in denervated muscle potentially increases myofiber vulnerability to corticosteroid injury *(96,97)*. In another animal model, dexamethasone (in comparable doses employed in human therapeutics) was injected into rats following denervation of the gastrocnemius muscle; this produced selective loss of thick (myosin) filaments and reduced muscle twitch amplitude, similarly to the abnormalities observed in humans with CIM *(97)*. These changes were not observed following either denervation or steroid treatment alone. Others have replicated these findings and demonstrated that myosin depletion can be reversed by re-innervation and discontinuing corticosteroids *(98,99)*. Importantly, withdrawal of dexamethasone alone was not sufficient to allow recovery; re-innervation was required to reverse the loss of thick filaments. The timing of recovery in this animal model is similar to the clinical course observed in patients with CIM *(43)*.

Glucocorticoids have been shown to activate an ATP–ubiquitin-dependent proteolytic system during the fasting state *(100)*. Minetti and associates *(101)* demonstrated that in two patients with CIM (one exposed only to steroids and one treated with steroids and NMBs), there was ubiquitin activation and myosin degradation and suggested that a ubiquitin-mediated pathway may play a role in the proteolysis and muscle fiber atrophy in CIM. Others have demonstrated overexpression of ubiquitin, caspases, and calpain (catabolic enzymes involved in protein degradation) along with induction of transforming growth factor-β and mitogen-activated protein kinase pathways in muscle biopsy material, suggesting that abnormal calcium homeostasis or apoptosis has a role in the pathogenesis of myosin loss in this illness *(85,102)*.

Some investigators have postulated a "two-hit" hypothesis to explain the etiology of CIM *(5,8,22)*. Steroids may act in a catabolic or some other novel way on the upregulated glucocorticoid receptors resulting from the functional denervation produced

by NMB; prolonged immobility may be a contributing factor *(84)*. Confirmation of this concept is demonstrated in a case reported by Panegyres and associates *(103)*, wherein a myasthenic patient with markedly elevated acetylcholine receptor antibodies developed an acute, severe myopathy following treatment with high-dose methylprednisolone. Muscle biopsy showed selective depletion of thick filaments. They postulated that a similar functional denervation, in this instance caused by acetylcholine receptor antibodies, rendered skeletal muscle susceptible to the myotoxic effects of corticosteroids *(103)*.

An alternative hypothesis suggests there is an alteration of the muscle membrane resting potential, ion channel inactivation, and reduced conductance, perhaps induced by high-dose corticosteroid administration or the effects of combined muscle denervation and steroid exposure *(104)*. As previously noted, Rich and colleagues *(80,105)* reported muscle membrane inexcitability following direct muscle stimulation in patients with CIM. It has been postulated that in patients with CIM, there is an abnormality of the regulation of muscle protein expression or stability, or an aberrant depolarization of the resting muscle membrane potential resulting from abnormal regulation of chloride or sodium channels and reduced sodium conductance *(104)*. Depolarization of muscle membrane could inactivate sodium channels, thus producing muscle inexcitability *(80,104,105)*. The observation that acute corticosteroid administration decreases muscle fiber conduction velocity, possibly because of changes in intracellular ion concentration, supports this view *(106)*. An animal model of CIM demonstrated that muscle fibers exposed to high-dose corticosteroids became inexcitable because of a hyperpolarizing shift in the voltage dependence of fast inactivation of sodium channels *(107,108)*.

Another theory suggests that CIM reflects a catabolic disorder of muscle that occurs as a consequence of sepsis and release of cytokines or other pro-inflammatory substances leading to muscle protein degradation *(30,87,109)*. Hypermetabolism in critically ill patients in the ICU leads to a catabolic state and subsequent muscle wasting and weakness, a condition known as cachectic myopathy *(30,33,110,111)*. The nature of this disorder is not well-defined; nerve conduction studies, EMG, and CK levels are normal, and muscle biopsy may either be normal or show type II fiber atrophy, consistent with disuse atrophy. Moreover, this hypothesis does not explain the occurrence of CIM in nonseptic patients.

Treatment

There is no specific therapy for CIM beyond supportive care. It seems prudent to avoid NMB agents in these patients and to taper corticosteroids as rapidly as their condition allows. Prognosis is generally favorable; those with mild limb weakness usually recover and wean from ventilator support within days or weeks after stopping corticosteroids and NMB agents. Patients with severe weakness often recover after several weeks or months, and although acute rehabilitation strategies seem intuitive, there have been no well-performed studies to indicate that aggressive physical therapy hastens recovery.

Rhabdomyolysis

Rhabdomyolysis may be a cause of weakness in critically ill patients. Common causes include muscle trauma (usually crush injury), ischemia of large muscle compartments from arterial compression or occlusion, sepsis, and, occasionally, medication or toxic ingestion. For example, acute necrotizing myopathy is a complication of treatment with cyclosporin A in transplant patients in the ICU and may develop after exposure to zidovudine in patients with AIDS *(112–114)*. Most patients with rhabdomyolysis have severe muscle pain and varying degrees of generalized weakness; complete paralysis is rare. Muscles are usually tender upon palpation and may appear swollen. Markedly elevated CK levels may lead to myoglobinuria and renal failure. Treatment is supportive and includes discontinuing treatment with the offending agent, hydration, alkalization of the urine (when myoglobinuria is present), and pain control.

Other Myopathies

Rarely, patients with undiagnosed myopathy may develop acute respiratory failure requiring ICU management, and occasionally, decompensation can be rapid and preclude prompt recognition of the underlying condition. There are numerous reports of respiratory failure as the initial manifestation of acid maltase deficiency, polymyositis, dermatomyositis, mitochondrial myopathy, and myotonic dystrophy *(115–118)*. Patients with the latter condition in particular may develop progressive weakness and respiratory decompensation after general anesthesia or a minor surgical procedure. Occasionally, patients with polymyositis or dermatomyositis have a fulminant presentation with rapidly progressive generalized weakness and severe myalgias. Other inflammatory myopathies that may be encountered in the ICU include acute viral myositis, acute alcoholic myopathy, HIV myopathy, and sarcoid myopathy *(34)*.

Disorders of the Neuromuscular Junction

Prolonged Neuromuscular Blockade

Prolonged neuromuscular blockade occurs when synaptic transmission remains impaired and weakness persists after NMBs have been discontinued. The duration of "prolonged" is difficult to define and may be as brief as minutes or hours after a single dose; it can be clinically important in postoperative patients who cannot be extubated. In the ICU setting, prolonged neuromuscular blockade typically occurs after repeated boluses or continuous infusions of NMBs, resulting in persistent weakness even when the drug is stopped. The duration of weakness in reported cases ranges from as little as hours to as long as 42 days *(83,119–136)*. These estimates are determined by the time to clinical recovery, not by direct assessment of neuromuscular function, and probably are confounded by other processes, such as poor cooperation resulting from sedation, encephalopathy, medication effects, and pain, or the presence of CIM or CIP. Most reports of weakness that has been attributed to prolonged neuromuscular blockade have not included detailed EMG studies or muscle and nerve biopsies to exclude other disorders, and serial assessment of neuromuscular transmission was not routinely performed. Therefore, it is difficult to critically evaluate many of these cases as the distinction between CIP, CIM, and other disorders becomes uncertain.

Patients require NMBs to facilitate mechanical ventilation; manage increased intracranial pressure; reduce muscle contraction associated with tetanus, drug overdose, or status

Table 3
Features of Prolonged Neuromuscular Blockade

Patients have primary parenchymal respiratory failure: COPD, asthma, ARDS
Intermittent bolus or continuous infusion of NMB, usually longer than 6 days
Flaccid, areflexic quadriplegia
Ptosis, ophthalmoparesis, facial diplegia
Impaired/absent spontaneous respirations
Normal sensation
Transient reversal of weakness after neostigmine
Abnormal train of four: reduced "twitch" amplitude
EMG: motor potentials may be absent with complete neuromuscular blockade
Fibrillations potentials may be prominent—"pharmacological denervation"
Repetitive nerve stimulation (2 Hz):abnormal decrement (>10%) of motor amplitude

COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; NMB, neuromuscular blockers.

epilepticus; or eliminate movements that interfere with diagnostic or therapeutic procedures performed at the bedside *(136–138)*. Pancuronium, vecuronium, and atracurium are the most commonly used NMBs in the critical care setting *(136–138)*. These agents compete with acetylcholine and bind to the α-subunit of the postsynaptic receptor concentrated at the motor end-plate. Pancuronium and vecuronium are aminosteroid compounds and may be myotoxic (as previously discussed), especially when combined with corticosteroids. There are fewer reports of neuromuscular complications with atracurium, a benzylisoquinolinium compound, although this may be explained by its less frequent use *(65–69,83)*.

Prolonged neuromuscular blockade was first described in 1963 in a patient with renal failure who was treated with gallamine and experienced paralysis for 5 days after the drug was discontinued *(128)*. In subsequent reports, all patients who developed this syndrome in the ICU have been paralyzed with NMBs for at least 2 days, but most have been treated for 6 days or more, and some received NMBs for weeks *(18,121–123,131)*. When the drugs are discontinued, a flaccid, areflexic quadriplegia persists, often with ptosis and ophthalmoplegia. A few have preserved eye movements, but ophthalmoplegia is so rare in CIM or CIP that it almost always signifies prolonged neuromuscular blockade (Table 3). Severely affected patients may have no spontaneous respirations, whereas others have mild generalized weakness and are unable to wean from ventilator support. Sensation is normal in the absence of CIP. The paralysis can sometimes be reversed with neostigmine or edrophonium, but this effect is transient. Weakness resolves after several days in most patients and persists as long as 1 or 2 weeks in a few, but virtually all patients recover completely. A more protracted recovery probably reflects CIM or CIP erroneously attributed to prolonged neuromuscular blockade *(66,121–123,130,131)*. The process has been reported in children and infants *(121,123,131,133)*.

Some predisposing factors associated with prolonged neuromuscular blockade have been delineated. Initial reports suggested an association with the cumulative dosage of NMBs or duration of treatment, but one study failed to confirm this association *(2)*. In 16 critically ill patients who were administered vecuronium, 7 developed prolonged neuromuscular blockade. All had negligible vecuronium levels, but those with prolonged paralysis had high concentrations of a vecuronium metabolite known as 3-desacetyl vecuronium *(2)*. This metabolite has 50 to 70% of the neuromuscular blocking potency of vecuronium and is believed to accumulate in patients with renal failure *(139,140)*. The association of renal failure and prolonged neuromuscular blockade has been previously described *(124,126,127,132)*. Segredo and colleagues *(2)* suggested that other factors also are linked to prolonged neuromuscular blockade, including female gender, acidosis, and hypermagnesemia. Because electrophysiological evaluation was performed in only one patient in their study, and no patients had muscle or nerve biopsies, the possibility remains that CIP or CIM contributed to the weakness in some patients. In other reports, many patients also received corticosteroids *(121,123, 125,130,135,141–143)*.

Other factors known to prolong the duration of NMBs in critically ill patients include advanced age, hepatic failure, certain medications (e.g., aminoglycosides, cyclosporine, clindamycin, lidocaine), electrolyte abnormalities, the combination of NMBs from different structural classes (aminosteroid and benzylisoquinolinium), and, possibly, concurrent sepsis *(122, 132,144–147)*. One study demonstrated that recovery time is faster with continuous infusion of pancuronium compared to intermittent bolus injection *(148)*.

EMG studies in this illness confirm a disorder of neuromuscular transmission in most cases and exclude a myopathy or neuropathy *(7,8,17,120,122,128,143,149)*. Repetitive nerve stimulation at 2 Hz shows a characteristic decrement in the amplitude of the CMAP, which reflects diminished acetylcholine binding at the postsynaptic receptor. This decrement has the same basis as the reduction of twitch amplitude following TOF stimulation. However, repetitive nerve stimulation can be relatively insensitive in establishing a neuromuscular junction disorder; for example, a decremental response is observed in only two-thirds of patients with generalized myasthenia gravis *(150)*. Furthermore, the correlation between abnormalities with TOF and repetitive nerve stimulation has not been studied. A recent study indicated that TOF monitoring did not lead to improved recovery time or lower NMB dose compared to clinical assessment *(151)*.

Single-fiber EMG is a technique with greater sensitivity to neuromuscular transmission disorders but is highly specialized and time-consuming. A derivative of this technique, stimulated single-fiber EMG, does not require patient cooperation but is still painstaking and has not been widely used in an ICU setting. CMAP amplitudes are usually low, but conduction velocities and distal latencies are normal or only mildly abnormal. If neuromuscular blockade is complete, then the CMAP may be absent, thus simulating a neuropathy; however, sensory potentials are normal. Needle examination shows diffuse fibrillation potentials, reflecting "pharmacological denervation" *(28,130,143)*.

Pathology

There are few pathological studies of patients with prolonged neuromuscular blockade. Immature neuromuscular

junctions with poor postsynaptic differentiation; short, unbranched junctional folds; and shallow secondary clefts were observed in muscle biopsies from two patients with prolonged weakness following neuromuscular blockade *(49)*. Preterminal motor axons were normal, but there was excessive sprouting of intramuscular nerves. A muscle biopsy obtained from an infant with persistent weakness following pancuronium administration demonstrated enlarged axon terminals that were deficient in acetylcholine vesicles but were engorged with organelles and neurofilaments *(135)*. One-half of the presynaptic axons were severely atrophic. Weakness in this case was attributed to a reversible, terminal motor axonopathy, a concept that has not been resolved and implies nerve damage (neuropathy), as discussed later *(135)*.

Pathogenesis

The role of corticosteroids in patients with prolonged neuromuscular blockade is controversial. Aside from its immunological and catabolic effects, corticosteroids have direct actions at the neuromuscular junction. The mini-end-plate potentials that are constantly elicited by leakage of acetylcholine into the synapse increase in frequency but decrease in amplitude in the presence of steroids, suggesting that steroids have a pre- and postsynaptic effect *(152,153)*. This reduction in amplitude may cause failure to reach the threshold required for an action potential, thereby impairing neuromuscular transmission. This effect may also explain the reason that patients with myasthenia gravis worsen transiently after initiating high-dose steroid treatment. In fact, Miller et al. *(154)* and others *(155)* demonstrated that steroids directly impair neuromuscular transmission in patients with myasthenia gravis. However, Schwartz and associates *(156)* showed that steady-state twitch tension of the adductor pollicis remained unchanged after corticosteroids were administered to 25 peri-operative patients who received NMBs, and they concluded that steroids had no interaction with NMBs.

Conversely, corticosteroids have been shown to potentiate or antagonize pancuronium-induced neuromuscular blockade in animal studies *(157–160)*. In one animal model, Kindler and colleagues *(161)* demonstrated that methylprednisolone inhibits muscle-type nicotinic acetylcholine receptors, and the effect was potentiated following the combined application of vecuronium and corticosteroids. However, in patients who received high doses of vecuronium without corticosteroids, there was substantial upregulation of the number of acetylcholine receptors, indicating that exposure to NMB agents alone induced morphological changes of the muscle membrane as well as functional denervation *(162)*. Furthermore, there is no direct clinical evidence that steroids independently contribute to impaired neuromuscular transmission in patients in the ICU who are administered NMBs. Currently, it must be concluded that steroids may have a limited influence in potentiating neuromuscular blockade in the ICU.

Some investigators have suggested that the main clinical and EMG features of patients with prolonged neuromuscular blockade indicate that the locus of damage is in the distal axon, rather than at the neuromuscular junction—especially in patients with normal repetitive stimulation and preserved sensory potentials *(18,21,121,125,135,143)*. This assertion probably relates to the insensitivity of repetitive stimulation testing and confusion between prolonged neuromuscular blockade and subtle CIP or CIM. Patients with prolonged weakness related to a distal motor axonopathy probably represent a variant of CIP *(21,31,32)*.

Despite its relative insensitivity, repetitive nerve stimulation is the most practical method for detecting prolonged neuromuscular blockade in the ICU. If a CMAP can be elicited in a clinically affected limb, repetitive stimulation or TOF remains the best method to establish the diagnosis and monitor recovery. In the absence of a decremental response, the diagnosis of prolonged neuromuscular blockade should remain in doubt.

The American College of Critical Care Medicine recently provided clinical practice guidelines for the use of NMB agents in adults *(138)*. These guidelines include (a) specific indications for the use of NMBs (manage ventilation and increased intracranial pressure, treat muscle spasms, etc.) only after other interventions have failed; (b) pancuronium is generally the preferred agent, but in patients for whom the vagolytic effects of this drug are contra-indicated (e.g., cardiac disease) and for those with significant hepatic or renal disease, cisatracurium or atracurium is recommended; (c) TOF should be used regularly to monitor the degree of blockade, with the goal of adjusting the dosage to produce one or two muscle twitches; (d) sedatives and analgesics should be used liberally in conjunction with NMB agents; (e) every effort should be made to discontinue NMB agents in patients who are treated with corticosteroids; and (f) drug holidays (daily attempts to stop NMB agents until the condition of the patient requires their use).

Treatment

As previously noted, virtually all patients eventually recover from prolonged NMB once the offending agent has been discontinued, but prolonged paralysis leads to a longer ICU stay and possibly increases the risk of patients developing CIM or CIP.

Other Disorders of the Neuromuscular Junction

Myasthenia Gravis

In some patients with myasthenia gravis, the condition develops in an accelerated or explosive fashion over days or weeks and leads to severe limb or oropharyngeal weakness or ventilatory failure. These patients require close monitoring, and a rapid reduction in the vital capacity below 15 cc/kg is an indication for intubation and mechanical ventilation. Occasionally, patients with undiagnosed myasthenia gravis have another condition (e.g., pneumonia, trauma, etc.) that requires ICU management or ventilator support; the neuromuscular condition is recognized only after the patient fails to wean from the ventilator *(163–165)*. Most patients have characteristic features of ptosis, ophthalmoparesis, and weakness of the neck flexor and limb muscles. The diagnosis is established with low-frequency repetitive nerve stimulation (2 Hz), tensilon test, or demonstration of elevated anti-acetylcholine receptor antibodies.

Lambert–Eaton Myasthenic Syndrome

Lambert–Eaton myasthenic syndrome is an auto-immune disease with auto-antibodies directed against presynaptic, voltage-gated calcium channels on the motor terminals of the

neuromuscular junction. The majority of cases are associated with small cell lung cancer or other malignancies. The condition is usually chronic with features of proximal weakness, dry mouth, impotence, and other manifestations of dysautonomia and areflexia; however, patients with an unrecognized myasthenic syndrome have presented with respiratory failure requiring intubation *(166)*. These patients improved with plasma exchange, pyridostigmine, prednisone, and 3,4-diaminopyridine *(166)*.

Botulism

Botulism is a rare condition that begins with cranial nerve dysfunction followed by generalized paralysis and can be confused with the oropharyngeal or ophthalmoparetic regional variants of GBS. The illness usually begins hours to days after the ingestion of the neurotoxin produced by Clostridium botulinum types A, B, or E through contaminated food. Nausea and vomiting are followed by constipation and neurological symptoms. Blurred vision is an early complaint. Initial findings include dilated pupils with paralysis of accommodation, ptosis, and oropharyngeal weakness. Diaphragmatic weakness with ventilatory failure is common and may be more severe than limb weakness. In contrast to GBS, the deep tendon reflexes are usually preserved. EMG shows reduced amplitudes of the motor potentials, with an incremental increase of the amplitude (usually >200% above baseline) following high-frequency repetitive nerve stimulation, indicating a presynaptic neuromuscular junction abnormality. The cerebrospinal fluid (CSF) is normal. The detection of botulinum toxin in the serum, contaminated food source, or culture of Clostridium botulinum from the stool confirms the diagnosis.

Miscellaneous Conditions

Antibiotics (especially aminoglycosides) and other medications may have deleterious effects on the neuromuscular junction but are seldom solely responsible for generalized weakness in the ICU *(114,167,168)*.

Disorders of Peripheral Nerve

Critical Illness Polyneuropathy

Bolton and colleagues *(9–15)* published a series of reports describing an axonal sensorimotor polyneuropathy associated with sepsis and multi-organ failure, which they termed CIP. In a prospective study of patients in the ICU, at least 70% had this form of acquired polyneuropathy when studied electrophysiologically, but only half had detectable weakness *(35,169,170)*. Others have also confirmed the high frequency of this condition in patients in the ICU who experience septic shock *(171)*. These patients were severely ill with bacteremia, acidosis, and hypoalbuminemia, and most were septic with hypotension and impaired kidney, liver, or other organ function. As the episode of sepsis resolved, difficulty weaning as a result of respiratory muscle weakness became apparent. From studies in the literature by Bolton et al. and others, a clinical picture has emerged of distal limb weakness, with hyporeflexia or flaccid, areflexic quadriplegia in severe cases. (refs. *1,9–22,23,24,27–29,* and *31–35*; Table 4). Approximately one-third of patients have retained reflexes *(9–22,29,32)*. There have been variable sensory deficits reported as a result of difficulties in testing critically ill, ventilated patients. Occasionally, patients experienced mild facial weakness, but ophthalmoparesis has been uncommon.

Table 4
Features of critical illness polyneuropathy.

Generalized weakness:(variable severity)
Mild distal leg weakness
Severe quadriplegia, flaccid limbs
Muscle atrophy
Distal sensory loss (may difficult to assess)
Facial and ocular nerves generally spared (no ptosis)
Hyporeflexia or areflexia
Reflexes may be obtained in one-third of patients
Ventilatory failure: failure to wean with impaired respiratory mechanics
EMG: reduced or absent motor and sensory potentials, no demyelinating features (excluding typical GBS); active denervation with poorly recruited motor unit potentials with normal configuration (early findings within days or weeks of symptom onset), or poorly recruited, neurogenic motor unit potentials (later findings detected months after symptom onset)
Cerebrospinal fluid: no cells, normal protein and glucose
Nerve biopsy: axon loss;no inflammation or demyelination
Muscle biopsy: neurogenic atrophy;features of critical illness myopathy may also be present

EMG, electromyography; GBS, Guillain–Barré syndrome.

As sepsis and organ failure resolve, the neuropathy often improves after weeks or months; some patients with a mild or moderate neuropathy experience complete recovery, whereas severely affected patients have residual, and probably permanent, weakness *(31,172–175)*. Several longer-term follow-up studies have demonstrated that the prognosis for complete recovery is not as favorable as initial reports have suggested *(175)*. Zifko *(173)* evaluated 19 patients with CIP after an average of 17 months following ICU discharge; 6 died in the first year, and 11 of 13 survivors had persistent neurological deficits and reduced quality of life. Similarly, in another study of 19 patients with severe CIP who were evaluated 2 years after hospital discharge, 11 experienced complete recovery, and the remaining 8 patients (33%) died or had persistent weakness *(174)*. The duration of fever (presumably associated with sepsis), number of days in the ICU, and amount of weight loss correlated with a poor recovery *(174)*. Superimposed entrapment neuropathies resulting from inadvertent compression or poor positioning also may have contributed to persistent deficits in patients with severe CIP *(173–175)*.

Older studies have found a strong correlation between the severity of the neuropathy and duration of ventilator dependence, severity of multi-organ failure, and number of different organs involved *(35,172,176)*. However, others have found no correlation between electrophysiological abnormalities and length of stay in the ICU or time on the ventilator. *(177)*. Some researchers have suggested that the peripheral nervous system is simply another organ involved in patients in the ICU with multiple organ dysfunction syndrome *(31,169,176)*. Some investigators have observed a significantly higher mortality in patients with CIP compared to patients in the ICU with similar APACHE III scores but who did not have neuropathy

(172,176,178); however, this finding has not been confirmed by others *(35)*. A prospective study of 73 patients with sepsis demonstrated that patients with CIP required ventilator support for an additional 12 days (median value), remained in the ICU an additional 19 days, and remained in the hospital an additional 52 days compared to patients without neuropathy *(178)*. The risk of in-hospital mortality was seven times greater among patients with CIP. Risk factors linked to CIP on multivariate analysis included hyperosmolality, parenteral nutrition, exposure to NMBs, and the absence of renal replacement therapy *(178)*. Another prospective study of 98 patients in the ICU confirmed that the risk of CIP was associated with higher APACHE III scores and the presence of systemic inflammatory response syndrome *(179)*.

The EMG demonstrates reduced motor and sensory amplitudes with relative preservation of conduction velocities and distal latencies consistent with an axonal sensorimotor polyneuropathy *(1,9–22,28,29,31–35)*. These changes have been observed as early as 3 days after onset of sepsis or ICU admission *(171,179)*. In contrast to GBS, there is no conduction block or segmental slowing of conduction velocity, and the spinal fluid protein is normal or only slightly elevated *(12)*. Although facial nerve paralysis is uncommon in CIP, one investigator observed denervation of the facial muscles in almost half the cases *(29)*. As many as 40% of patients with CIP have been reported to have a pure motor axonopathy with preserved sensory nerve action potentials *(21,77,177,181–183)*. However, the existence of a pure motor form of CIP remains controversial in the absence of larger studies that exclude CIM and have contemporaneous muscle histopathology *(75,79)*.

Electrophysiological assessment of the respiratory system can be helpful in establishing the diagnosis of CIP *(35,177)*. The amplitude of the CMAP elicited by phrenic nerve stimulation is greatly reduced or absent in 50 to 80% of cases and correlates with the presence of ventilatory failure *(35,177)*. The EMG shows abnormal spontaneous muscle activity in proximal and distal limb muscles and poorly recruited motor units that, together, are consistent with the expected active denervation from an acute polyneuropathy. Active denervation also has been observed in the diaphragm and other respiratory muscles in patients with CIP and failure to wean *(35,177,184)*. Repetitive nerve stimulation is consistently normal, an important finding that virtually excludes prolonged neuromuscular blockade *(15,34,183)*. However, serial studies of stimulated single-fiber EMG have demonstrated abnormal jitter with acute denervation in some patients with CIP, indicating an abnormality of the terminal motor axon *(182)*. In patients who recover from sepsis, nerve conduction studies usually demonstrate improved compound muscle action potential amplitudes and re-innervation changes after several months.

Pathology

Histological studies of nerve obtained at autopsy or nerve biopsy have confirmed that there is axonal degeneration of distal motor and sensory nerves, without inflammation or primary demyelination *(13)*. Chromatolysis of anterior horn cells and degeneration of dorsal root ganglion cells have also been observed as secondary phenomena. The muscle has shown denervation atrophy, but occasional necrotic fibers, vacuoles, and increased glycogen deposition have been observed, suggesting a concurrent CIM *(13,77,183)*.

Pathogenesis

The mechanism of CIP is not understood, and some investigators have attributed it to the nonspecific effects of altered microcirculation related to sepsis *(33)*. For example, Bolton and colleagues and others have hypothesized that proinflammatory cytokines (including tumor necrosis factor [TNF], serotonin, or histamine) are released during sepsis and increase microvascular permeability, leading to breakdown of the blood–nerve barrier, endoneurial edema, and hypoxia *(13,18,33,169)*. This is supported by increased expression of E-selectin within endoneurial vessels, indicating abnormal endothelial cell activation, which may occur as a consequence of sepsis *(185)*. Additional theories include: (a) axonal degeneration resulting from glucose-induced phosphate depletion from parenteral nutrition, with subsequent depletion of high-energy phosphate compounds *(186)*; (b) damage of neural microvasculature resulting from oxidative effects of parenterally administered lipids *(187)*; (c) impaired transport of axonal proteins or reduced transmembrane potentials *(33,77)*; and (d) toxic effects from release of proinflammatory cytokines. *(33,77,90)*. For example, researchers have demonstrated that TNF decreases the resting transmembrane potential of skeletal muscle fibers in vitro and induces muscle proteolysis in animals *(188)*. However, one study failed to show elevated levels of TNF or interleukin-6 in patients with CIP *(189)*. Druschky et al. and others presented preliminary data identifying a low-molecular-weight substance derived from the sera of patients with CIP; this substance was toxic to rat spinal motor neurons *(190,191)*. Other studies have failed to implicate vitamin or nutritional deficiencies, electrolyte abnormalities, or medications, all of which were former explanations for persistent weakness in patients in the ICU *(169)*. It has been determined that the severity of CIP corresponds to the duration of ICU stay as well as serum glucose levels, as previously noted *(169,180)*.

Although sepsis and multi-organ failure have been closely associated with CIP, in some cases, steroids and NMBs may also have a role. One patient in the study by Bolton et al. received a combination of dexamethasone and pancuronium *(9)*. Subsequent reports from that group failed to comment on the use of steroids or NMB, but others have reported CIP in patients treated with high-dose steroids, NMBs, or both, without sepsis or multi-organ failure *(17,18,21,143)*. For example, Op de Coul and colleagues *(18)* reported that 20 of 22 patients with CIP had received NMBs, but only 11 were septic. They attributed weakness to a complication of NMBs, but the patients were heterogeneous and probably included cases of CIP, CIM, and prolonged neuromuscular blockade. Kupfer and coworkers *(143)* observed five patients with a predominantly motor neuropathy and two with prolonged neuromuscular blockade following a continuous infusion of vecuronium. None had sepsis or multi-organ failure. Surprisingly, one prospective study of patients in the ICU failed to show any relationship between CIP and sepsis, multi-organ failure, steroids, or NMBs *(59)*. Although many authorities in the field have stressed a

causal relationship between sepsis and CIP, reports from other investigators have suggested that sepsis is not invariably required *(1,21,32,179)*. For example, a review of 142 cases of CIP found that infection was an infrequent primary diagnosis for ICU admission, accounting for only slightly more than one-fourth of the patients *(32)*. This probably underestimates the frequency of sepsis that occurs after ICU admission in patients who develop CIP, but others have cared for patients with typical CIP in whom infection was not a complicating factor *(17,18,21,59,143)*. De Letter and colleagues *(179)* noted that the sepsis severity score was not greater in patients with CIP compared to those patients without CIP. Clinicians should be willing to make the diagnosis of CIP in patients with severe systemic illness or multiple organ dysfunction when the characteristic clinical and electrophysiological features are present—even in the absence of sepsis. In cases of generalized weakness, confounding variables and a poor understanding of the pathophysiology of CIP should deter clinicians from prematurely dismissing other contributing factors.

Treatment

There is no effective therapy for CIP. However, in a group of critically ill patients in a surgical ICU, intensive insulin therapy that maintained blood glucose at or below 110 mg/dL substantially reduced the risk of developing CIP; there was a linear correlation between the risk of polyneuropathy and the mean blood glucose level *(180)*. A recent prospective, randomized controlled trial showed a 50% reduction of the frequency of CIP in critically ill patients treated with intensive insulin therapy *(192)*. The median number of days on mechanical ventilation and number of patients who required more than 2 weeks of mechanical ventilation was also substantially reduced *(192)*. An open-label trial of intravenous immunoglobulin (IVIg) in three patients showed no benefit *(193)*, but another report indicated that the frequency of CIP was reduced in septic patients who were administered IVIg early in their ICU course, suggesting that IVIg may ameliorate or prevent CIP from developing in high-risk septic patients *(194)*.

Guillain–Barré Syndrome

Many large series of patients with GBS have contained a small proportion of cases that reportedly occurred after surgery *(195)*. Some of these patients most likely had CIP as a consequence of multi-organ failure, sepsis, or other factors associated with a prolonged postoperative course in an ICU, but a few cases of GBS genuinely may have been triggered by an operation *(196)*. There are at least three well-documented cases of GBS that became evident after discontinuing NMBs or corticosteroids in patients with status asthmaticus *(197–199)*. Two received large doses of hydrocortisone or methylprednisolone, and one required NMBs for 10 days but did not receive steroids. They had severe flaccid, areflexic quadriplegia, and two required prolonged ventilator support. The spinal fluid protein was normal, but the EMG showed conduction block or temporal dispersion, prolonged distal latencies, or absent F-responses, all of which are characteristic of an acquired demyelinating polyneuropathy. Repetitive nerve stimulation and nerve or muscle biopsies were not performed. The immune nature of the process is further suggested by improvement in two patients following plasma exchange *(197,198)*. Another patient who developed areflexic quadriparesis after multi-organ failure had an elevated CSF protein, elevated anti-GM1 antibodies, prolonged F-responses, and widespread denervation and most likely had an axonal variant of GBS *(200)*.

Acute Intermittent Porphyria

A few notable conditions are associated with acute generalized weakness that occasionally may be encountered in the ICU setting. Patients with acute intermittent porphyria (AIP) may develop a neuropathy resembling GBS *(201)*. Various medications or infections can trigger an acute attack. Initial symptoms include vomiting, constipation, and abdominal pain. Seizures occur in 10 to 20% of cases and delirium or other psychiatric symptoms occur in most. The weakness is symmetric and begins in proximal muscles of the arms, but as the syndrome progresses, widespread weakness develops in most patients. Hypertension, arrhythmias, or other features of dysautonomia are common. The cranial nerves are typically spared. EMG shows an axonopathy rather than demyelination, thus differentiating this condition from GBS. Increased urinary excretion of δ-aminolevulinic acid and porphobilinogen during an acute attack of AIP establishes the diagnosis.

Vasculitic Neuropathy

Neuropathy is a common complication of systemic vasculitis and usually evolves in a subacute fashion; rarely, acute mononeuritis multiplex has a fulminant course and simulates an acute polyneuropathy *(202)*. Polyarteritis nodosa and Churg–Strauss syndrome are the vasculitides that are most likely to cause a rapidly progressive polyneuropathy and may be associated with multi-organ involvement (especially renal or pulmonary insufficiency) requiring ICU management. In most cases, focal or multifocal onset, severe pain, lack of cranial nerve involvement, and electrophysiological features of a multifocal axonopathy distinguish acute vasculitic neuropathy from GBS, CIP, and CIM. The CSF protein level is normal in vasculitic neuropathy, and the diagnosis is established by pathological evidence of vasculitis on biopsy material.

Disorders of the Motor Neuron

Amyotrophic Lateral Sclerosis

Isolated diaphragmatic weakness with progressive ventilatory failure is an uncommon variant of amyotrophic lateral sclerosis *(34,73,203)*. These patients develop progressive dyspnea with physical activity, eventually leading to breathlessness at rest and, ultimately, retention of carbon dioxide and acute ventilatory failure. These individuals may be intubated in the emergency room before a diagnosis is established, and a neurologist is consulted days or weeks later, after the patient fails to wean from the ventilator. There may be mild oropharyngeal and limb weakness, but these findings often are inconsequential compared to the respiratory abnormalities. In patients who are not intubated, there is rapid, shallow breathing with an increased respiratory rate; use of accessory muscles of respiration; paradoxical movements of the chest wall and abdomen; and reduced vital capacity, tidal volume, and negative inspiratory force. These patients are at high risk for

aspiration. The diagnosis is established by electrodiagnostic studies that show widespread active denervation, fasciculations, and chronic re-innervation in several limbs, respiratory muscles and, often, muscle groups that are clinically unaffected. The amplitude of the phrenic nerve CMAP is usually reduced, and needle electrode examination of the diaphragm shows active denervation. Sensory potentials are normal *(73,203)*.

Acute Flaccid Paralysis: West Nile Virus Infection

West Nile virus (WNV) is an arthropod-born flavivirus first isolated in 1937 in the West Nile region of Uganda. Over the subsequent six decades, there have been numerous human epidemics documented in the Middle East, South Africa, Russia, and the United States *(204)*. The virus first appeared in the United States in 1999 in New York City and has since spread westward; WNV has been reported in all but three states, triggering the largest human arboviral encephalitis epidemic in US history (ref. *205*).

Ecology and Epidemiology

The WNV genome is a single-stranded RNA within the Japanese encephalitis antigenic complex. The virus is maintained in an enzooic mosquito–bird–mosquito cycle. Thirty-seven species of mosquitos have been shown to harbor the virus, but most human infections have occurred following bites from the *Culex* species or from other so-called "bridge vectors" (mosquitos that feed on birds and humans). Almost 85% of human infections occur in August and September, coinciding with the peak of the mosquito–bird transmission; however, year-round transmission is possible in tropical climates. Birds serve as the amplifying host and spread the infection to new regions; most human epidemics in the United States are temporally linked to prior high avian mortality. A total of 146 species of bird have been infected with WNV, and crows and blue jays are especially susceptible *(206)*. Conversely, humans and horses are considered "dead-end" hosts because of low-level and brief duration viremia *(206)*. However, during the 2002 epidemic, person-to-person transmission was reported through blood transfusion, organ transplantation, intra-uterine infection, and, possibly, through breast milk *(207)*. Infections have also been documented in laboratory personnel via inadvertent inoculation *(208)*.

Most human infections are asymptomatic. Approximately 20% of infected individuals develop West Nile fever, an influenza-like illness manifest by high fever, malaise, myalgias, and headache. Only 1 in 150 patients infected with WNV develop neurological symptoms *(209)*. There is no gender or age predilection, but older individuals (over age 50 years) have a higher risk of developing the febrile illness and neurological disease *(210)*. Other risk factors include length of time spent outdoors, failure to use mosquito repellent, and the presence of mosquitos in the home *(209)*.

Clinical Features

Three clinical patterns of neurological disease from WNV infection have emerged: West Nile meningitis, West Nile encephalitis (WNE), and acute flaccid paralysis (AFP). Substantial overlap among the syndromes may occur, because over half of patients with WNE in the New York City outbreak experienced severe weakness *(210)*. For example, a recent review of 23 cases of WNV from Cleveland, Ohio indicated that 17% of patients had WNE followed by AFP, and 26% had a combination of all three patterns *(211)*. Presenting features of WNV infection are fever (87–100%), fatigue (65%), altered mental status (57–100%) occasionally progressing to coma, headache (44–100%), and back and limb pain (35–40%) *(205)*. Associated systemic features include nausea, abdominal pain, myalgias, transient maculopapular rash (50%), and lymphadenopathy. In those with WNE who later develop AFP, weakness usually begins within a few days to a week after hospitalization. The median duration of ICU admission in these patients is 10 days *(211)*. Isolated AFP is the presenting feature of WNV infection in 4 to 18% of cases *(211,212)*. Weakness has a predilection for proximal muscles and is usually asymmetrical. Patient may develop monoplegia, paraplegia, brachial diplegia, or quadriplegia that progresses over hours to several days. Reflexes usually are preserved or brisk but may be absent in clinically affected limbs. Sensation is normal. Bladder dysfunction occurs in a few cases. Bulbar weakness and ventilatory failure occur in a minority of patients *(213–215)*, and ophthalmoparesis is rare *(216)*.

Diagnostic Studies

There may be a mild leukocytosis or leukopenia, and hyponatremia is frequently observed. Other routine laboratory studies usually are normal *(217)*. CSF studies show an elevated protein level (range: 51–899 mg/dL), lymphocytic pleocytosis (range: 0–1782 cells/mm^3), and normal glucose levels *(217,218)*. The diagnosis is confirmed by detection of IgM antibody to WNV in the serum or CSF. The IgM antibody capture enzyme-linked immunosorbent assay test is the preferred method, but serum IgM antibodies may not be detected until at least 8 days following acute infection *(218)*. Serum IgM antibodies may persist for 6 months or longer, and, therefore, detection of high titers may reflect a previous infection that is unrelated to the current illness *(218)*. Head computed tomography scans are usually normal, and brain magnetic resonance imaging (MRI) shows meningeal or ventricular enhancement in approximately one-third of cases. MRI of the spine may demonstrate signal change in the anterior horn cells (refs. *211,217–219*; Figure 3).

Electrodiagnostic studies confirm a motor neuron disorder in most cases. The CMAPs are reduced or absent, conduction velocities and distal motor latencies are normal or slowed in proportion to the degree of axon loss, and there is no conduction block. Sensory potentials are almost always normal. Needle electrode examination shows fibrillations with reduced recruitment in a segmental (myotomal) pattern *(211,213,215, 219)*. There are rare reports that WNV infection may be associated with demyelinating features suggesting GBS *(220)*. Similarly, those who have isolated AFP frequently have been misdiagnosed with GBS, but these conditions usually can be distinguished by the absence of fever and encephalopathy, symmetrical weakness, prominent sensory symptoms, generalized areflexia, lack of pleocytosis in the CSF, and prominent demyelinating features on EMG studies in patients with GBS. Notably, several other RNA viruses can produce a

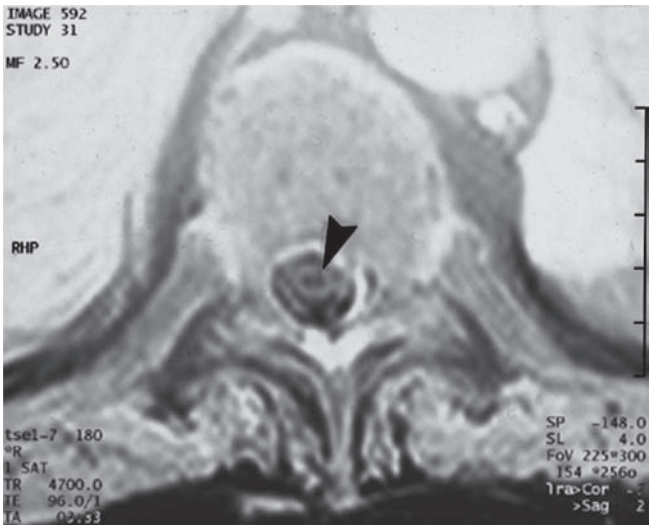

Fig. 3. Axial spin-echo image of the thoracic spinal cord in a patient with West Nile virus infection and acute flaccid paralysis. Note the signal change in the anterior horns of the spinal cord (arrowhead).

poliomyelitis syndrome that has superficial similarities to AFP or a motor axonal variant of GBS *(221)*.

Pathology and Pathogenesis

The pathogenesis of AFP is unknown, but it has been suggested that WNV, similar to poliovirus, has neurotropism for the anterior horn cells of the spinal cord, which also has been observed in monkeys, horses, and birds in experimental animal studies *(218)*. Autopsy studies have confirmed lymphocytic infiltration of anterior horn cells ($CD3^+$, $CD4^+$, and $CD8^+$ T cells), with striking loss of motor neurons, chromatolysis, and microglial nodules as well as detection of viral antigens in the spinal cord using immunohistochemical stains *(211,216,222)*.

Therapy and Prognosis

There is no specific therapy for AFP, and treatment is supportive. High-dose ribavirin and interferon (IFN)-α-2b were effective against WNV in vitro, but no controlled data from human trials are available *(218)*. A few patients with encephalitis and cerebellar involvement and one patient with AFP reportedly improved following treatment with IFN-α-2b *(223)*. IVIg has been used anecdotally, and without benefit, in a few patients with AFP *(219)*. There is an ongoing clinical trial of IVIg in patients with WNE or AFP sponsored by the National Institutes of Health *(224)*. A recent study suggested that passive administration of IVIg containing anti-WNV antibodies to infected mice can prevent or reduce the severity of WNV infection *(225)*. One case report concluded that high-dose steroids are useful *(226)*.

The case fatality rate is 10 to 12%, and risk factors for death include older age, reduced level of consciousness, paralysis, and immunosuppression *(218)*. Patients with AFP generally have a poor prognosis; most have little or no improvement of limb weakness *(212,215,219)*, although some patients may have severe but transient focal weakness that resolves completely within a few weeks *(215)*.

Other Paralytic Syndromes

Clinicians must remember that there are central nervous system disorders that cause generalized paralysis that may mimic neuromuscular disease. Myelopathies, including those caused by tumor compression, trauma, inflammation (myelitis), and ischemia, can affect all the limbs and respiration if they are situated in the high cervical region. In the initial stages, the reflexes may be muted from spinal shock, thus simulating a neuromuscular problem; however, a careful sensory examination will reveal a spinal sensory level with a change from reduced or absent to normal sensation below the clavicles. Spinal cord disease should always be a concern when generalized paralysis does not include the facial muscles. Basilar artery occlusion that damages the corticospinal fibers in the pons also causes generalized paralysis that may extend to the face and eye movements. Most patients have risk factors for stroke, a history of preceding transient ischemic attacks, and specific neurological features such as preserved vertical gaze, hyperreflexia, and the presence of Babinski signs.

Conclusions

CIM, prolonged neuromuscular blockade, and CIP are the three main neuromuscular syndromes that produce prolonged paralysis in patients in the ICU. More than one syndrome may occur simultaneously, and the distinctions may be difficult in a particular patient *(35,77,175)*. Nonetheless, in most cases, one process predominates, and the precise neuromuscular syndrome usually can be delineated after careful clinical, electrophysiological, and histological evaluation *(227–229)*. Asthmatics with generalized weakness who received a combination of steroids and NMBs most likely have CIM, whereas patients who have had a prolonged ICU stay or sepsis and multi-organ failure with failure to wean from the ventilator probably have CIP. All of the syndromes can produce a severe, flaccid, areflexic quadriplegia, but proximal weakness and preserved reflexes favor a myopathy, whereas predominant distal weakness, objective sensory loss, and areflexia suggest CIP. Ptosis and ophthalmoparesis occur with prolonged neuromuscular blockade and are rare with CIM or CIP. Impaired sensation, although difficult to confirm in an ICU setting, strongly implicates CIP. The CK level is typically, but not uniformly, elevated in myopathy; however, it is usually normal in CIP and prolonged neuromuscular blockade. Patients admitted to the ICU with fever and encephalopathy followed by asymmetric, flaccid paralysis should be evaluated for WNV infection.

Electrodiagnostic studies with repetitive nerve stimulation clarify the diagnosis in most cases and are indicated in any patient in the ICU who experiences unexplained weakness. The EMG should be considered as an extension of the clinical examination with a specific electrodiagnostic question to be addressed. Direct muscle stimulation is a promising technique that may distinguish CIP from CIM. The results of the EMG can be confusing when more than one process occurs simultaneously, and in this situation, a muscle and/or nerve biopsy should be obtained to establish the diagnosis. The biopsy specimen (muscle or nerve) should be selected based on the results of the EMG and must be interpreted by experienced individuals.

Because there is no specific therapy for these neuromuscular syndromes, attention has necessarily focused on prevention. For example, intensive insulin therapy to maintain blood glucose below 110 mg/dL reduces the risk of CIP. Twitch monitoring has been suggested as a mandatory test in patients receiving NMBs, but most physicians currently use this technique infrequently, and there is no evidence that serial testing with TOF prevents neuromuscular complications *(26,122–124,136–138,143,147,151,230)*. Instead, the use of NMBs should be minimized *(138)*. Most critically ill patients requiring assisted ventilation can be managed adequately with the use of short-acting benzodiazepines (midazolam), propofol, and analgesics (fentanyl, morphine). Moreover, there is strong evidence that corticosteroids should not be administered concurrently with NMBs. If NMBs are necessary, a shorter acting, nonsteroidal agent (atracurium) may be preferable *(138)*. If possible, NMBs should be discontinued daily to assess for neurological recovery, and continuous infusions and prolonged duration of treatment (>48 hours) should be avoided *(138)*. TOF monitoring may prevent inadvertent overdosing as well as excessive neuromuscular blockade in some patients. Most importantly, clinicians caring for critically ill patients must have an awareness of the frequency of neuromuscular complications associated with these agents.

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