Acute Weakness Syndromes in the Critically Ill Patient

James A. Sliwa, DO
Rehabilitation Institute of Chicago, Chicago, IL 60611


Over the past three decades there has been increasing interest in acute weakness syndromes in critically ill, mechanically ventilated patients. Initially described in 1974 when 10 children with acute asthma were found to experience motor weakness, these acute weakness syndromes have not been well understood. In 1983, an acute motor neuropathy, named “critical illness polyneuropathy,” was described in patients with sepsis and multiple organ failure.1 In 1985, an association was noted between certain drugs, namely neuromuscular blocking agents, used to facilitate mechanical ventilation, and aminoglycoside antibiotics and acute weakness.2 By 1987, the contribution of high-dose corticosteroids in conjunction with neuromuscular blocking agents to the occurrence of weakness in critically ill patients was appreciated, and by 1991 myopathy of intensive care was described.3 The potential causes for these acute weakness syndromes are quite extensive and include disorders of the peripheral nerves, the neuromuscular junction, and muscle.3 This article will review commonly encountered causes of acute weakness in critically ill patients, including disorders of the peripheral nerves, the neuromuscular junction, and muscle.

Over the past three decades there has been increasing interest in cases of profound muscle weakness in critically ill, mechanically ventilated patients. Initially described in 1974 when 10 children with acute asthma were found to experience motor weakness, these acute weakness syndromes have not been well understood. In 1983, an acute motor neuropathy, named “critical illness polyneuropathy,” was described in patients with sepsis and multiple organ failure.1 In 1985, an association was noted between certain drugs, namely neuromuscular blocking agents, used to facilitate mechanical ventilation, and aminoglycoside antibiotics and acute weakness.2 By 1987, the contribution of high-dose corticosteroids in conjunction with neuromuscular blocking agents to the occurrence of weakness in critically ill patients was appreciated, and by 1991 myopathy of intensive care was described.3 The potential causes for these acute weakness syndromes are quite extensive and include disorders of the peripheral nerves, the neuromuscular junction, and muscle.2,3 This article will review commonly encountered causes of acute weakness in critically ill ventilated patients. Many of these patients require rehabilitation, and some understanding of possible causes and outcomes is useful to those providing care to this population.

CRITICAL ILLNESS POLYNEUROPATHY (CIN)

Knowledge of the association between neuropathy and sepsis spans a century since Osler described wasting as a complication of sepsis. The association of sepsis, multiple organ failure (critical illness), and peripheral neuropathy has become more definitely established within the past few decades. Historically, however, understanding of this neuropathy has been limited by the many terms that have been used to describe it, including “coma-polyneuropathy” and “intensive care unit neuropathy,” and its confusion with other known causes of potential weakness in critically ill patients such as Guillain-Barré syndrome.4

CIN is one nervous system manifestation of sepsis, the earliest component of which is septic encephalopathy. Within hours of a positive finding on blood culture, impaired attention, concentration, orientation, and writing ability are apparent.5 Symptoms can progress and usually precede signs of polyneuropathy. Difficulty with weaning from the ventilator is usually the earliest sign of CIN. Typically, weakness then becomes apparent, involving distal muscles more than proximal. However, depending on the severity of neurologic involvement and the time course of the illness, tetraplegia may be present. Muscle stretch reflexes typically are reduced, and in many cases sensory loss occurs.5-10 In patients with evidence of sepsis and multiple organ failure, the incidence of peripheral nerve abnormalities can be as high as 70%, with clinical signs of peripheral neuropathy occurring in approximately half of these.11

The morphologic features of CIN have been demonstrated through peripheral nerve biopsy and autopsy studies of both the central and the peripheral nervous systems.4 Findings are consistent with primary axonal degeneration of peripheral motor and sensory fibers, without evidence of inflammation. Inspection of muscle shows scattered atrophic fibers in acute denervation and group atrophy in chronic denervation. Occasional necrotic muscle fibers have also been found.4,6,7,8 Electrophysiologic findings are consistent with primary axonal loss. The earliest findings are a reduction in the amplitude of the compound muscle and sensory action potentials, with only minor changes in distal latencies, conduction velocities, and F-wave latencies. Needle studies typically reveal acute denervation with positive waves and fibrillation potentials.4,7 Signs of denervation of chest wall muscles and reduced or absent phrenic nerve conduction will confirm respiratory muscle weakness due to neuropathy as the cause of difficulty in weaning the patient from the ventilator. Motor unit potentials, if they can be activated, will often appear normal but sometimes can present with low amplitudes and a polyphasic nature, consistent with a primary myopathy. However, a diminished sensory compound action potential amplitude confirms peripheral nerve involvement.4 Repetitive nerve stimulation in cases of CIN is usually normal. In severe cases, progression of axonal loss typical of CIN will ultimately result in demyelination with slowing of conduction, and what began as a pure axonal peripheral neuropathy may take on a “mixed” axonal and demyelinating picture.

CRITICAL ILLNESS MYOPATHY (CIM)

Relatively recently, myopathies have been recognized as a cause of weakness developing in patients who are being cared for in the intensive care unit. The discovery of muscle...
pathology as the cause of diffuse, generalized weakness in critically ill patients began with the observation of weakness and difficulty in weaning patients from the ventilator after the use of neuromuscular blocking agents. This problem was first described by Hunter in 1956 as “neostigmine resistant curarization” and was first appreciated by anesthesiologists as a short-term complication of anesthesia lasting hours after the effect of the medication was reversed with neostigmine.13 In many cases, this short-term persistent paralysis was due to the accumulation of the neuromuscular blocking agent or its metabolites in patients with renal failure or hepatic dysfunction.14 The extended use of neuromuscular blocking agents in critically ill patients to assist with ventilation has led to many reports of severe and prolonged weakness. Op de Cool and associates15 observed 12 patients in whom tetraparesis developed after prolonged use of pancuronium to assist in ventilation. Recovery of muscle strength took as long as 5 months, in some patients recovery was incomplete, and in others weakness persisted. Kupfer and associates reported on 10 asthmatic patients who required vecuronium infusion for paralysis to assist in ventilation during an acute attack. Two of these patients experienced short-term weakness, and five had diffuse generalized weakness lasting as long as several months. Since then, many similar cases have been described, and common to all has been the use of either corticosteroids or neuromuscular blocking agents, or in most cases both.17 Although muscle biopsy confirmed the presence of primary muscle involvement, reports vary concerning the type of muscle pathology identified. Some describe muscle necrosis and degeneration of type I and II fibers and elevated serum creatine kinase levels,18,19 while others report rare necrosis, atrophic muscle fibers, and extensive loss of thick myofilaments.20,21 Many terms, such as “critical care myopathy,” “acute quadriplegic myopathy,” “myopathy of asthma,” “acute myopathy of intensive care,” and “critical illness myopathy” have been applied to this entity. The myopathy associated with critical illness and use of corticosteroids and neuromuscular blocking agents can be either an acute necrotizing myopathy or an acute myosin filament loss myopathy. Acute necrotizing myopathy is characterized by severe weakness, generalized in nature, with occasional ophthaloplegia that can last weeks to months. Patients typically are areflexic, with normal sensation and marked elevation of the serum creatine kinase level. These patients will have experienced prolonged use of neuromuscular blocking agents and usually concomitant use of high-dose corticosteroids.3 On electrophysiologic studies, conduction velocity is typically normal, with reduction in the compound muscle action potential (CMAP) amplitude and relative sparing of the sensory nerve action potential (SNAP) amplitude. Abnormal spontaneous activity is seen with early recruitment of small, short-duration polyphasic motor unit potentials on needle examination.3

Acute myosin filament loss myopathy is characterized by moderate or severe, predominantly proximal limb and respiratory weakness. Cranial nerve deficits are uncommon, and sensory deficits are not typically noted. Tendon reflexes are reduced or absent, and serum creatine kinase levels are normal or only slightly and transiently elevated. This myopathy appears to be associated with exposure to high doses of corticosteroids with or without concomitant use of neuromuscular blocking agents. Findings on nerve conduction studies are similar to those seen in necrotizing myopathy, with normal velocities, reduced CMAP amplitudes, and relative sparing of SNAP amplitudes. On electromyography, little or no spontaneous activity is seen and both normal and small, brief polyphasic motor unit potentials appear.3 Differentiation of CIM from CIN can be difficult because of overlapping circumstances that lead to their development and their similar presentation. This can be especially true in the intensive care unit when symptoms are first observed. Direct muscle stimulation has been proposed to help differentiate CIM from CIN. On the basis of findings that muscle retains normal excitability in peripheral neuropathy and is inexorable in critical illness myopathy, Rich and associates22 prospectively studied 14 weak critically ill patients with this technique. Recording the CMAP via nerve and direct muscle stimulation, they calculated a nerve-to-muscle ratio. This technique, the authors concluded, can help differentiate critical illness myopathy from neuropathy in severely weak, critically ill patients.22

In some cases of CIM in which high-dose corticosteroids have been used in conjunction with prolonged neuromuscular blockade, components of both necrotizing and myosin filament myopathy have been observed. Likewise, if sepsis and multi-organ failure have also been a component of the clinical picture, features of CIN can be present and may explain the neuromyopathy reported in critical illness. Consequently, it may be most appropriate to consider CIN and CIM as less distinct clinical entities than typically described.

ETIOLOGY OF CRITICAL ILLNESS POLYNEUROPATHY AND MYOPATHY

It is possible that CIN results from disruption of blood to distal axons as part of the systemic inflammatory response syndrome that occurs with sepsis.4 Also postulated to occur in cases of major trauma and burn, the systemic inflammatory response syndrome results in release of cytokines and in the activation of lymphocytes, monocytes, and neutrophils. Cytokines may increase capillary permeability, with endoneural edema resulting. Furthermore, capillary blood flow becomes obstructed by platelet aggregates and adhesion molecules adhering to leukocytes and endothelial cells. As a result of these changes, organ parenchyma are deprived of essential oxygen and nutrients and the result is multiple organ failure. It is the changes from the sepsis-induced systemic inflammatory response syndrome, producing disruption of the microvascular blood flow, that results in the distal axonal degeneration and is believed to cause critical illness neuropathy.4

Thick myosin filament loss myopathy appears to result from the combined use of corticosteroids and neuromuscular blocking agents. Selective loss of thick filaments has been produced experimentally in animals by combining mechanical denervation and high doses of corticosteroids. The combination of high-dose corticosteroids and neuromuscular blocking agents and the resulting myopathy appear
analogous to the mechanisms and pathology in these animal studies and suggests a common etiology. Furthermore, denervation of rat skeletal muscle leads to a marked increase in the number of glucocorticoid receptors in the muscle, suggesting that denervated muscle may be highly susceptible to corticosteroids and that denervation, either through neuropathy or from neuromuscular blockade coupled with corticosteroid use, may lead to a severe steroid-induced myopathy. 

Whether the systemic inflammatory response syndrome contributes to myopathy is not known. Bolten has postulated that through the increased capillary permeability potentially associated with this syndrome, neuromuscular blocking agents could have a direct toxic effect on nerves, resulting in a relatively pure motor neuropathy. Muscle denervation resulting from this motor neuropathy, CIN, and/or the denervation resulting from the use of neuromuscular blocking agents would all render muscle susceptible to the effects of concomitantly administered corticosteroids. Increased capillary permeability could also facilitate steroid access to this denervated muscle, resulting in thick myosin filament loss myopathy with varying degrees of necrosis.

RECOVERY OF FUNCTION AFTER CRITICAL ILLNESS POLYNEUROPATHY AND MYOPATHY

Much of the focus to date in patients who have acute weakness after having survived a critical illness has been on identifying the diagnosis and understanding the pathophysiology of CIN or CIM. Less has been written about physical recovery and motor return. Recovery from CIN typically depends on the degree of nerve involvement. Witt and associates reported that in mild cases recovery can be expected in weeks, in severe cases months; in especially severe cases, deficits may be permanent. Jarret and Mogelof described the functional improvements in four patients with CIN admitted for rehabilitation. These results appear to support the long-term recovery of patients with CIN. Op de Cool and colleagues described a retrospective review of 22 patients with CIN. Forty-five percent of patients had complete recovery of motor function within 1 year (average 4.5 months), 18% had incomplete recovery, and 37% died. Fifty patients less than 75 years of age who were admitted to the intensive care unit and mechanically ventilated for more than 7 days were evaluated with electrodiagnostic studies by Leitjen and associates to test the hypothesis that prolongation of motor recovery after ventilation is due to polyneuropathy. The main functional outcome measures were a return to normal strength and an ability to walk 50 meters independently. Twenty-nine of 50 patients (58%) satisfied electrodiagnostic criteria for polyneuropathy. Of these 29 patients, 22 showed predominantly features of axonal injury, with positive waves and fibrillation potentials on needle examination, and diminished amplitudes of muscle and nerve action potentials. In half of the axonal polyneuropathies (11 patients), distal latencies were prolonged and conduction velocities were slowed (“mixed” polyneuropathy), whereas in the other half distal latencies and conduction velocities were normal (“pure axonal” polyneuropathy). In the remaining seven patients, generalized slowing was seen on electrodiagnosis with no signs of axonal injury, as evidenced by a lack of spontaneous activity on the electromyogram. Thirty-two patients survived the intensive care period, and 24, all of them free of secondary causes of impairments, were evaluated for functional outcome. Twelve of these patients had electrodiagnostic evidence of polyneuropathy when studied in the intensive care unit and 12 did not. Nine of the 24 patients did not return to normal motor function and independent ambulation of 50 meters within 4 weeks of intensive care discharge. Eight of these nine patients had polyneuropathy. At 1 year, five patients were left with severe deficits, all five displaying conduction slowing on electrodiagnostic studies in the intensive care unit, and four of the five with mixed polyneuropathy (evidence of axonal loss and conduction slowing). The authors concluded that prolonged mechanical ventilation is associated with the development of a polyneuropathy. In most cases this is an acute axonal, predominantly motor neuropathy defined as CIN. However, with severe axonal injury and demyelination, recovery appears to be slow and is sometimes incomplete.

Less is known about motor return and functional recovery after CIM. Munin and associates described two patients with vechuronium-induced tetraparesis who underwent inpatient rehabilitation. Both patients displayed significant functional improvements in all areas of self-care and mobility and improvements in muscle strength over their rehabilitation course following rehabilitation stays of 3 and 7 weeks. We also have followed the recovery of 11 patients who required mechanical ventilation, high-dose intravenous corticosteroids, and in all but one case a neuromuscular blocking agent. All had primary lung disease (asthma and chronic obstructive pulmonary disease) that prompted hospitalization, and none experienced sepsis or additional organ failure. All had difficulty with weaning from the ventilator, and all had weakness so severe that mobility and self-care were impaired, so that inpatient rehabilitation was required. Each of these patients’ clinical picture was consistent with a diagnosis of CIM. As compared with CIN, motor and functional return appears to be quite favorable. The average length of hospital stay for these 11 patients was 21 days, with a range of 8 to 39 days. Muscle strength improved an average of one grade in the upper and two grades in the lower extremities on manual muscle testing. We utilized the 13 motor items of the Functional Independence Measure to assess the degree of functional independence at admission and discharge. These items, which include feeding, grooming, bathing, upper and lower extremity dressing, toileting, bowel and bladder function, bed, toilet and tub transfers, ambulation, and stair climbing, are graded on a scale of 1 to 7. All patients made significant functional improvement, with nine patients having discharge Functional Independence Measure scores of 80 or better (maximum possible score is 91). Two patients, the most severely impaired on admission, with Functional Independence Measure scores of 31 and 29, were discharged with scores less than 80. It appears that the prognosis for recovery after CIM is good, with those who were more severely involved being more likely to experience prolonged or incomplete recovery.
GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is a common cause of acute generalized weakness, with an annual incidence of 0.75 to 2.0 cases per 100,000 population. An estimated 5,000 new cases per year are diagnosed in the United States. It is postulated that some patients admitted to the intensive care unit may represent undiagnosed cases of GBS; in others, the syndrome may develop in response to the illness that precipitated the admission. In typical cases, however, the initial manifestations of GBS are paresthesias and motor weakness, which can, in severe cases, progress to tetraparesis. Cranial nerve involvement can result in loss of eye movement, facial weakness, and swallowing difficulties. Respiratory compromise requiring mechanical ventilation can occur. Autonomic dysfunction can result in heart rate abnormalities, fluctuating blood pressure, anhidrosis, or periodic diaphoresis.

When fully developed, the typical clinical picture is one of symmetric weakness associated with diminished or absent reflexes, paresthesias, and, in many cases, some degree of sensory loss. About two-thirds of cases develop after an infection, which is usually viral in nature. Typically, flu-like upper respiratory tract infections are most common, followed in frequency by gastrointestinal illnesses. Known viral precipitants include Epstein-Barr and cytomegalovirus. Mycoplasma pneumonia and Lyme disease have been associated with a GBS-like illness, although bacterial infections are rarely associated with the illness. Other antecedent events associated with GBS include immunizations, surgery, epidural anesthesia, and underlying concurrent illnesses such as systemic lupus erythematosus, Hodgkin’s disease, sarcoidosis, and human immunodeficiency virus infections. Campylobacter jejuni enteritis has recently been recognized as an important antecedent infection, which appears to be associated with a more severe axonal form of the disease.

This axonal form, termed “acute motor axonal neuropathy,” is clinically indistinguishable from acute inflammatory demyelinating GBS, with the exception of its being characterized by normal sensory functions. An acute motor-sensory axonal neuropathy has also been identified.

Acute GBS typically presents with paresthesias in the toes and fingers, followed by symmetric lower extremity weakness that ascends and ultimately involves the upper extremities. Pain is a common finding early in the presentation. Progression of symptoms usually occurs over 10 to 12 days, and more than 50% of patients reach the nadir of their symptoms by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks. It is very unusual to see worsening of symptoms after 1 month. Clinical findings that could have been observed to progress over time and support a diagnosis of GBS could be obscured during a prolonged period of intubation or sedation required for the treatment of an intercurrent medical event.

GBS is thought to be an inflammatory polyradiculoneuropathy. Lymphocytes and macrophages, with a predilection for the nerve roots, surround endoneural vessels and cause demyelination. Antibodies to various gangliosides have been shown in a number of GBS patients and in many but not all with evidence of Campylobacter jejuni infection. In the acute motor axonal neuropathy and acute motor-sensory axonal neuropathy patterns, axonal involvement is predominant, with wallerian-like axonal degeneration of nerve fibers with minimal inflammation and demyelination. On microscopy, macrophages are seen in the periaxial space surrounding or displacing the axon and surrounded by an intact myelin sheath.

The hallmark of GBS is evidence of demyelination on electrodiagnostic testing. Although studies may initially be negative, abnormalities typically appear, starting with prolongation of F-wave latencies and H-reflexes, and then including prolongation of distal latencies, slowing of conduction velocities, reduced amplitude and temporal dispersion of the CMAP, and partial or complete conduction block. Abnormalities on sensory studies typically lag behind the motor abnormalities. In severe cases, fibrillation potentials and positive sharp waves can develop, indicating some degree of secondary axonal damage. Electrophysiologic diagnostic criteria for the demyelinating version of the disease have been established. In the acute motor axonal variant, electrodiagnostic findings are consistent with axonal loss and include early fibrillation potentials and positive sharp waves and reduction in the amplitude of the CMAP. Conduction velocities and distal latencies remain normal, as do sensory functions.

Plasma exchange has been established as an effective treatment for acute GBS. Randomized, controlled trials of plasma exchange have shown that the procedure decreases the duration of required mechanical ventilation and the time until ambulation. Benefits were diminished if treatment began 2 weeks after onset of the illness. Intravenous gamma globulin given within the first 2 weeks has also been beneficial. In one prospective, randomized trial, gamma globulin was shown to be as effective as plasmapheresis in the treatment of acute GBS.

Recovery over weeks to months is the typical pattern in GBS. Fifteen percent of patients will have no apparent residual deficits. Permanent disabling weakness, imbalance, or sensory loss occurs in only 5% to 10%. The majority of patients return to functional independence despite minor neurologic residual effects. Poorer prognosis is associated with older age at onset, need for ventilator support for more than 1 month, severe and rapidly progressive disease, and evidence of axonal loss.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

Many medications commonly used in an intensive care unit, such as muscle relaxants, aminoglycoside antibiotics, and some antiarrhythmics, can precipitate weakness and functional loss in undiagnosed cases of disorders in neuromuscular junction transmission (table 1). Consequently, these disorders should be considered as a cause of new weakness in critically ill patients. Two syndromes that result from dysfunction of neuromuscular junction transmission, Lambert-Eaton myasthenic syndrome and myasthenia gravis, will be discussed here.
Lambert-Eaton Myasthenic Syndrome

Patients with Lambert-Eaton myasthenic syndrome usually complain of nonspecific weakness and exertion-induced fatigue. Lower-extremity proximal weakness is usually the presenting complaint, and patients describe difficulty in arising from a chair or climbing a long flight of stairs. Upper-extremity weakness affecting primarily the shoulder girdle is also common. On physical examination, muscle strength improves with continued contraction against resistance and worsens after prolonged activity. Reflexes may initially be diminished or absent but then become easier to obtain after contraction of the muscle. Sensory loss is rare, but some form of autonomic dysfunction is common. In 50% to 70% of patients, the syndrome is associated with some form of tumor. When tumors are present, more than 90% are located within the thoracic cavity. It is common for symptoms of the syndrome to precede discovery of a tumor. Lambert-Eaton myasthenic syndrome is believed to have an autoimmune basis, with antibodies targeting presynaptic calcium channels. Antibody binding with the calcium channels reduces calcium entry into the nerve terminal and thereby decreases the quantal content per vesicle and limits the release of acetylcholine into the synaptic cleft. On electrophysiological testing, sensory conduction velocity and amplitude are normal, motor conduction velocities are likewise normal but with marked reduction in the CMAP amplitude at rest is usually normal. Repetitive stimulation at slow rates typically results in a decremental response with amplitudes in the low-normal or below-normal range. At higher rates of repetitive stimulation or following brief exercise, the CMAP amplitude can be quite variable and may be normal, decremental, or occasionally incremental. On the electromyogram, a small percentage of patients with severe disease display positive sharp waves and fibrillation potentials, as muscles may be denervated by destruction of the neuromuscular junction. More commonly, motor unit action potentials may appear shorter in duration and smaller in amplitude than normal because of the dropout of single muscle fibers whose neuromuscular junctions have failed to depolarize. Treatment of myasthenia gravis typically employs the use of acetylcholinesterase inhibitors, immunosuppression, thymectomy, and plasma exchange.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder that results in diminished numbers of acetylcholine receptors, a widened synaptic space, and an altered postsynaptic membrane, all of which disrupt normal neuromuscular transmission. Persons with myasthenia gravis present with abnormal fatigability after extensive activity or at the end of the day. Weakness usually involves the external ocular, bulbar, and proximal limb muscles, and diplopia and ptosis are the most common initial complaints. Symptoms are usually gradual in onset and may progress over several years. The course of the illness, however, is quite variable, with rapid spread of muscle weakness in some whereas in others the disease can remain unchanged for months before progressing. Remissions occur in less than half of cases and seldom last for more than 1 or 2 months. Physical examination typically reveals normal sensation to all modalities and normal reflexes. Muscle testing should include frequently involved muscles, and the examiner should attempt to elicit fatigue after sustained activity. For example, sustained upward gaze or repeated eye opening and closing may elicit ptosis. Antibodies to acetylcholine receptors block the acetylcholine binding site and contribute to multiple changes, including a decreased number of receptors, destruction of the postsynaptic membrane, and widening of the synaptic cleft. As a result of these changes, blocking only a small number of acetylcholine receptors will, in myasthenia gravis, result in failure of the neuromuscular junction to generate a muscle contraction because of subthreshold excitation of the postsynaptic membrane. On electrodiagnostic testing, sensory nerve conduction velocities and amplitudes are normal, as are motor nerve conduction velocities. The CMAP amplitude at rest is usually normal. Repetitive stimulation at slow rates typically results in a decremental response with amplitudes in the low-normal or below-normal range. At higher rates of repetitive stimulation or following brief exercise, the CMAP amplitude can be quite variable and may be normal, decremental, or occasionally incremental. On the electromyogram, a small percentage of patients with severe disease display positive sharp waves and fibrillation potentials, as muscles may be denervated by destruction of the neuromuscular junction. More commonly, motor unit action potentials may appear shorter in duration and smaller in amplitude than normal because of the dropout of single muscle fibers whose neuromuscular junctions have failed to depolarize. Treatment of myasthenia gravis typically employs the use of acetylcholinesterase inhibitors, immunosuppression, thymectomy, and plasma exchange.

Table 1: Drugs That May Potentiate Neuromuscular Blocking Agents

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<td>Lidocaine</td>
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<td>Antibiotics</td>
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<td>Aminoglycosides (gentamicin, tobramycin, amikacin)</td>
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<td>Polypeptides (polymyxin B)</td>
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<td>Other antibiotics (clindamycin, tetracycline)</td>
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<td>Antiarrhythmics</td>
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<td>Magnesium</td>
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<td>Calcium-channel blockers</td>
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<td>Beta-adrenergic blockers</td>
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<td>Chemotherapeutic agents</td>
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<td>Dantrolene</td>
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<td>Diuretics</td>
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<td>Furosemide (biphasic response)</td>
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<td>Thiazides</td>
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<td>Lithium carbonate</td>
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<td>Cyclosporine</td>
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Porphyric Neuropathy

The porphyrias are disturbances in heme biosyntheses which result in intermittent episodes of nervous system clinical and electrical improvements are seen after use of certain medications, such as aminopyridine and 3,4-diaminopyridine, and in noncarcinomatous Lambert-Eaton myasthenic syndrome following therapy with corticosteroids and plasmapheresis.
dysfunction and/or skin sensitivity to sunlight. Neurologic manifestations result in abdominal pain, peripheral neuropathy, and mental disturbances. The peripheral neuropathy can rapidly progress to tetraparesis. Although pain may be present and sensory changes can occur, weakness is the cardinal symptom. There can be a variable picture of loss of muscle strength with weakness, beginning either proximally or distally in a symmetric or asymmetric pattern. Cranial nerve involvement can occur as the neuropathy progresses, and autonomic dysfunction manifested as tachycardia and blood pressure variations can be seen. Attacks can be precipitated by pregnancy, alcohol, lead, low-carbohydrate diet, infections, or certain drugs such as barbiturates and sulfonamides.

The neuropathy associated with porphyria appears to be an acute axonal neuropathy affecting primarily motor fibers. However, in about 50% of cases, sensory fibers are also involved. On electrodiagnostic studies, nerve conduction velocities are normal, with decreased CMAP amplitudes. Evidence of denervation, positive waves, and fibrillation potentials is present on the electromyogram. In patients who are critically ill and require mechanical ventilation, an attack of acute porphyria with severe and rapidly progressing weakness resulting in tetraparesis could be precipitated by an associated infection or by antibiotics administered during the course of their acute illness.

STEROID MYOPATHY

The long-term use of glucocorticoids has numerous associated side effects, including muscle weakness and atrophy. Muscle atrophy is induced through several cellular mechanisms. The inhibition of glucose uptake into skeletal muscle contributes to muscle protein breakdown. Direct stimulation of protein degradation and inhibition of protein synthesis also occur. This disruption of protein synthesis, including cellular proteins such as myosin, results from altered gene expression via specific steroid receptors within the cytoplasm of the muscle cell. In addition, glucocorticoids promote amino acid transport out of muscle for metabolic utilization. Acidosis appears to potentiate the effects of glucocorticoids on muscle protein catabolism.

Glucocorticoid-induced muscle atrophy is selective for type II muscle fibers. Clinically, weakness is usually of gradual onset, painless, and symmetric. Proximal muscles initially of the lower and then of the upper extremities are typically the first to display weakness. With time, muscles of the distal extremities also become involved. Resistance and endurance exercise training can attenuate but not eliminate glucocorticoid-induced muscle atrophy and weakness. Although often considered a potential cause of weakness in the critically ill, steroid myopathy usually has an insidious onset and is not the cause of acute muscle weakness.

Electrodiagnostic studies in cases of steroid myopathy typically show no abnormalities. Excessive glucocorticoids do not alter the peripheral nervous system, and consequently motor and sensory conduction studies are normal. The lack of abnormalities on the electromyogram is due to preferential involvement of type II fibers by glucocorticoids and the recruitment of type I fibers first during needle examination. If the disorder progresses and significant numbers of type I fibers are involved, the clinical picture may resemble myasthenic syndrome. The steroid myopathy is usually characterized by weakness of predominantly proximal muscles, with sparing of distal and extraocular muscles.

 ![Diagram](image-url)
fibers become involved, short-duration and small-amplitude motor unit potentials can be seen.39

DECONDITIONING

Patients who are critically ill commonly require prolonged bed confinement and inactivity during the management of their acute illness. Prolonged immobility can lead to significant muscle weakness and atrophy, with a loss of 1.0% to 1.5% of strength per day. A loss of 25% to 40% of total strength is possible with prolonged mobility.40 Type I fibers appear more subject to immobilization atrophy than type II fibers, and large antigravity muscles seem to lose more strength and at a faster rate than smaller muscles. Weakness is of more gradual onset and can result in poor coordination and quality of movement on resumption of activity. Atrophy of muscle fibers can result from disuse and is associated with decreased protein synthesis. In animal studies, immobilizing a muscle in the stretched position appears to decrease the amount of resulting atrophy.41

Maintenance of muscle strength during periods of immobility can be accomplished by the performance of muscle contractions of 30% to 50% of maximal tension for several seconds each day.41 Recovery of strength is variable and may take twice the period of immobilization. The degree of final recovery can depend on age, premorbid functional status, and coexisting neurologic, musculoskeletal, or other medical conditions. Electrodagnostic studies in patients with the deconditioning syndrome are normal, with the exception of decreased CMAPs in severely atrophied muscles.

CONCLUSION

The potential causes of acute weakness in the critically ill are quite varied and can represent dysfunction at any site along the neuromuscular axis. A clearer understanding of the specific pathology involving the peripheral nervous system, the neuromuscular junction, and muscle as a cause of acute muscle weakness has recently been delineated (fig 1). An organized approach to the investigation of these cases, including knowledge of the hospital course and medications used during acute care, findings on physical examination, and results of electrodagnostic testing, will help delineate etiology and prognosticative functional return.

References