CHAPTER 149

NEUROMUSCULAR DISORDERS

EDWARD VALENSTEIN • MATTHEW MUSULIN

Neuromuscular disorders are commonly encountered in the critical care setting. Patients with known neuromuscular disorders, such as Guillain-Barré syndrome or myasthenia gravis, are admitted when weakness compromises the patient’s ability to protect him or her airway or threatens ventilatory failure. Patients admitted with ventilatory failure of unknown cause may be diagnosed with a neuromuscular disorder such as amyotrophic lateral sclerosis or myasthenia gravis. Rarely, treatment may unmask a pre-existing neuromuscular disorder, as when drugs with neuromuscular blocking properties are given to patients with myasthenia gravis. Finally, patients with nonneuromuscular critical illnesses frequently develop neuromuscular weakness as a result of their illness or its treatment.

As with central nervous system (CNS) disorders, the first step in the diagnosis of neuromuscular disorders is localization. Neuromuscular disorders comprise disorders of the anterior horn cell, the peripheral nervous system (PNS), the neuromuscular junction, and muscle. Disorders of the PNS are further subdivided into disorders of roots, plexus, and peripheral nerve; and disorders of peripheral nerve are further subdivided into focal neuropathies, multifocal neuropathies, and polyneuropathies. Polyneuropathies, in turn, can be either length dependent or non–length dependent. Each of these nine major disease categories may be admitted for respiratory support before the cause is identified (Fig. 149.1).

Recognizing that a patient’s problem is related to a disorder of the peripheral nervous system, or muscle is relatively straightforward in patients who can give a history of their illness, and who can be adequately examined. If the problem is exclusively neuromuscular, features suggestive of central nervous system localization should be absent. These include mental status changes, hemibody weakness, or numbness suggestive of hemispheric or lateralized brainstem lesions; truncal motor or sensory level suggestive of spinal cord localization; increased muscle tone; hyperactive tendon reflexes; and pathologic reflexes such as the Babinski response. Features consistent with localization to the peripheral nervous system include weakness, atrophy, decreased or absent tendon reflexes, and sensory loss. Most acquired myopathies present with symmetric proximal weakness, and sensory loss is not a feature of either myopathy or disorders of neuromuscular transmission. Fatigable ptosis, weakness of extraocular movement, dysphagia, dysarthria, and neck, respiratory, and proximal limb weakness should suggest myasthenia gravis, the most common nonpharmacologic disorder of neuromuscular transmission.

Rarely, the presentation of a neuromuscular disorder may be so restricted as to first suggest a nonneuromuscular problem. Acute pansynautonomia presents with autonomic failure that can mimic cardiovascular, gastrointestinal, or urinary disorders. Diabetic truncal neuropathy can present with abdominal pain that often leads to extensive evaluation for nonneuromuscular abdominal disorders, including exploratory surgery. Respiratory failure can be the presenting feature of a number of neuromuscular diseases, including amyotrophic lateral sclerosis (ALS), myasthenia gravis, and myopathies such as adult-onset acid maltase deficiency.
Section XIV: Neurologic Disease and Dysfunction

NEUROMUSCULAR DISORDERS

Nerve

Neuromuscular Junction
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Botulism
Pharmacologic

Muscle
Inherited myopathies (muscular dystrophies, congenital myopathies, periodic paralysis)
Acquired myopathies (inflammatory, endocrine, toxic, critical illness myopathy [CIM])

Anterior horn cell: ALS, post-anoxic amyotrophy

Root: Herniated disk, spondylolisthesis, H. zoster, Lyme disease, neoplasm

Plexus: Idiopathic (autoimmune), trauma, diabetes, neoplasm, radiation

Peripheral nerve

Mononeuropathy: Entrapment, compression, trauma

Multifocal neuropathy (mononeuritis multiplex):
Facial palsies, autoimmune demyelinating

Polyneuropathy

Length dependent: Metabolic, toxic, nutritional, inherited, other

Non-length dependent: Autoimmune (acute = Guillain-Barré, chronic = CIDP), Critical illness polyneuropathy (CIP)

FIGURE 149.1. Localization of neuromuscular disorders, with the most important exemplars for each of the nine localizations. ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy.

understood; it is left to the intensive care physician to suspect the correct diagnosis.

Diagnosing neuromuscular disorders that develop in critically ill patients can be challenging, since the patients are often unable to provide a history or to cooperate with the examination. Neuromuscular problems are usually first suspected when patients recovering from critical illness cannot be weaned from the respirator or are not moving their limbs; both central and neuromuscular causes of weakness need to be considered. Central causes of weakness may be suggested by the history and physical examination. Hemiparesis should always suggest a central localization; however, bilateral weakness can also result from central causes. A history of severe hypotension suggests the possibility of bilateral watershed infarction (9); rapid correction of hyponatremia predisposes to central pontine myelinolysis (CPM), an osmotic demyelination syndrome that presents with bulbar weakness and quadriparesis (10); patients after cardiac surgery may have multiple cerebral emboli; and patients with aortic dissection may suffer spinal cord infarction. Brain imaging may help establish a diagnosis in stroke or CPM; in other conditions, such as hypoxia or even acute spinal cord ischemia, imaging may be normal or nondiagnostic. If the cause of apparent weakness remains in question, electrodiagnostic testing is of value in suggesting or helping to exclude a neuromuscular localization.
TABLE 149.1
SALIENT FEATURES OF NEUROMUSCULAR DISORDERS

<table>
<thead>
<tr>
<th>Localization</th>
<th>Pain</th>
<th>Sensory loss</th>
<th>Tendon reflexes</th>
<th>Distribution of weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Variable (myalgia)</td>
<td>No</td>
<td>Normal or ↓</td>
<td>Symmetric, proximal</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>EOM, bulbar, respiratory, proximal</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>No</td>
<td>No</td>
<td>↓</td>
<td>Bulbar, proximal</td>
</tr>
<tr>
<td>Lambert-Eaton</td>
<td>No</td>
<td>No</td>
<td>↓</td>
<td>Diffuse (begins focally); spaces EOMs, bladder</td>
</tr>
<tr>
<td>Nerve</td>
<td>No</td>
<td>No</td>
<td>↓</td>
<td>Diffuse (begins focally); spaces EOMs, bladder</td>
</tr>
<tr>
<td>Anterior horn cell</td>
<td>No</td>
<td>No</td>
<td>↓</td>
<td>Diffuse (begins focally); spaces EOMs, bladder</td>
</tr>
<tr>
<td>Root</td>
<td>Yes</td>
<td>Variable</td>
<td>Focally ↓</td>
<td>Root</td>
</tr>
<tr>
<td>Plexus</td>
<td>Yes</td>
<td>Variable</td>
<td>Focally ↓</td>
<td>Plexus</td>
</tr>
<tr>
<td>Mononeuropathy</td>
<td>Variable</td>
<td>Usual</td>
<td>Often normal</td>
<td>2 or more single nerves</td>
</tr>
<tr>
<td>Multiple mononeuropathy</td>
<td>Variable</td>
<td>Usual</td>
<td>Often normal</td>
<td>Single nerve</td>
</tr>
<tr>
<td>Length-dependent polyneuropathy</td>
<td>Variable</td>
<td>Usual</td>
<td>Distal (feet → legs → hands)</td>
<td></td>
</tr>
<tr>
<td>Non-length-dependent polyneuropathy</td>
<td>Variable</td>
<td>Variable</td>
<td>Often areflexic</td>
<td>Proximal as well as distal</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; EOM, extraocular muscle. The most important salient features are indicated in bold typeface.

Electrodiagnostic Studies

Although it requires the expertise of a physician trained in both the clinical and electrophysiologic diagnosis of neuromuscular disorders to decide what studies are appropriate and to interpret the results, it is important for the treating physician to appreciate how these studies can assist in diagnosis and management. Electrodiagnostic studies can help to answer the following questions:

1. Is there a neuromuscular disorder causing weakness?
2. Is this a disorder of nerve, neuromuscular junction, or muscle?
3. If there is a disorder of nerve, is the pathology primarily demyelinating or axonal?
4. What is the distribution of the deficits?

Motor Nerve Conduction Studies

Figure 149.2A illustrates the typical motor nerve conduction procedure and normal response from stimulation of the tibial nerve. The nerve is stimulated at two or more sites, and the response is recorded with surface electrodes over a muscle innervated by that nerve. The muscle response is called a compound muscle action potential (CMAP), because it is the sum of all muscle fiber action potentials activated by nerve stimulation. The stimulus at each site is gradually increased until no further increase in CMAP amplitude is seen. This indicates that all of the motor neurons capable of generating an action potential have been activated. The latency to the onset of the CMAP reflects the speed of conduction in the fastest nerve fibers. Motor nerve conduction velocity is calculated by measuring the distance between the sites of stimulation, and dividing that distance by the proximal minus the distal latency, which is the time it takes for the stimulus to traverse that nerve segment. By itself, motor nerve conduction can be diagnostic of focal or generalized demyelinating neuropathy (Fig. 149.2C,D). Interpreting a low-amplitude response (Fig. 149.2B) requires additional studies, since low CMAP amplitude can reflect not only loss of nerve axons or conduction block, but also defective neuromuscular transmission or loss of muscle fibers.

Sensory Nerve Conduction Studies

In orthodromic sensory nerve conduction studies, the skin is stimulated and a response is recorded over the nerve. Antidromic studies are more commonly performed by stimulating the nerve and recording over the skin. The result in either case is a sensory nerve action potential (SNAP), with a latency that reflects conduction in the fastest nerve fibers, and an amplitude that is proportional to the number of functioning nerve fibers. The normal SNAP amplitude is small and measured in microvolts. Abnormal SNAPs are indicative of pathology distal to dorsal root ganglion—either plexopathy or neuropathy. SNAPs are normal in radiculopathy if the pathology spares the dorsal root ganglia in CNS disorders as well as in disorders of neuromuscular transmission and muscle. In a patient with weakness and abnormal motor nerve conduction studies, small or absent SNAPs suggest sensorimotor neuropathy or plexopathy.

F-wave Studies

Action potentials in motor neurons are normally generated at the axon hillock and travel distally to nerve terminals in muscle; but when the nerve is stimulated in the course of nerve conduction studies, action potentials travel both orthodromically (distally) and antidromically (proximally) from the point
## Table 149.2

### Electrodiagnostic Features in Nonfocal Neuromuscular Disorders

<table>
<thead>
<tr>
<th></th>
<th>Anterior horn cell</th>
<th>Axonal neuropathy</th>
<th>Demyelinating neuropathy</th>
<th>Neuromuscular junction disorder</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor Nerve Conduction Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAP amplitude to distal stimulation</td>
<td>Small</td>
<td>Small</td>
<td>Larger than to proximal stimulation</td>
<td>Normal (MG) or small (MG, LEMS)</td>
<td>Normal or small</td>
</tr>
<tr>
<td>CMAP amplitude to proximal stimulation</td>
<td>Same as to distal stimulation</td>
<td>Same as to distal stimulation</td>
<td>Smaller than to distal stimulation</td>
<td>Same as to distal stimulation</td>
<td>Same as to distal stimulation</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>Over 70% LLN</td>
<td>Over 70% LLN</td>
<td>Can be &lt;70% LLN</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>F-Wave Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-wave latency</td>
<td>Normal or increased latency</td>
<td>Normal or increased latency</td>
<td>Absent or increased latency</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Sensory Nerve Conduction Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory nerve action potentials</td>
<td>Normal</td>
<td>Can be reduced (normal in pure motor forms)</td>
<td>Often reduced or absent (normal in pure motor forms)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Needle EMG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>MUP morphology</td>
<td>Normal or large</td>
<td>Normal or large</td>
<td>Normal or large</td>
<td>Variable MUP morphology</td>
<td>Small amplitude, polyphasic</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal or “increased”</td>
<td>Full recruitment produces little force</td>
</tr>
<tr>
<td><strong>Repetitive Stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3 Hz stimulation</td>
<td>Usually normal</td>
<td>Usually normal</td>
<td>Usually normal</td>
<td>&gt;10% decrement in MG, LEMS</td>
<td>Usually normal</td>
</tr>
<tr>
<td>20-50 Hz stimulation</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>&gt;50% increment in LEMS</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CMAP, compound muscle action potential (the potential recorded in motor nerve conduction studies); EMG, electromyography; MG, myasthenia gravis; LEMS, Lambert-Eaton myasthenic syndrome; MUP, motor unit potential.

The most salient features for each localization are indicated in bold typeface.

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of stimulation. The antidromic action potential depolarizes the axon hillock and, in a minority of neurons, this depolarization generates another action potential that travels orthodromically down the nerve. This produces a small, late, muscle action potential, called the F wave, which can be recorded from most muscles. Increased F-wave latency, when combined with normal distal motor nerve conduction, indicates disease in the proximal portions of the nerve. Abnormal or absent F waves are the earliest electrophysiologic manifestation of Guillain-Barré syndrome (11,12).

### Needle Electromyography

Needle EMG entails inserting a recording needle electrode into a muscle and observing (a) insertional activity consisting of action potentials generated by mechanical deformation of muscle fibers as the needle is inserted; (b) resting activity, which in normal muscles is only seen when the needle is near an end plate; and (c) voluntary activity, which consists of motor unit action potentials (MUPs). The motor unit consists of a motor neuron and all the muscle fibers innervated by it. The MUP is the sum of action potentials of all the muscle fibers in the vicinity of the recording needle electrode that are activated by a single motor neuron. Insertional and resting activity do not require patient cooperation, and can be observed in comatose or uncooperative patients. One to three weeks after denervation associated with axon damage, denervated muscle membranes become hypersensitive and discharge both spontaneously and in response to needle insertion, causing increased insertional activity and the appearance of positive sharp waves and fibrillations, which are spontaneous or needle movement–induced discharges of single muscle fibers. Similar abnormal spontaneous activity can be seen in disorders of muscle,
FIGURE 149.2. Typical motor nerve conduction findings. The sweep speed is 5 ms/div in all traces, but
the gain is 5 mV/div in A and C, 1 mV/div in B, and 500 μV/div in D. A: Tibial motor nerve conduction in
a normal subject. The drawing shows the two sites of stimulation over the posterior tibial nerve at the
ankle and knee, and the sites of surface electrodes recording the response of the medial planter muscle
group. The two waveforms are the responses to stimulation at the ankle and knee. Conduction velocity is
calculated as the distance between proximal and distal sites of stimulation divided by the time it takes for
the stimulus to travel between the sites of stimulation (PL minus DL). B: Tibial motor nerve conduction in
a patient with axonal sensorimotor neuropathy. CMAP amplitudes are less than 2 mV, with normal being
greater than 4 mV. The amplitudes are similar with proximal (knee) and distal (ankle) stimulation. The
conduction velocity is slightly slow, but is greater than 80% of the lower limits of normal. C: Peroneal
motor nerve conduction study in focal nerve compression. CMAP amplitude drops sharply with nerve
stimulation above the site of compression, at the fibular head. This conduction block is caused by focal
nerve demyelination. Because there is no damage to axons, the nerve responds normally to stimulation
distal to the area of demyelination. Conduction velocity is slow across the fibular head. D: Acquired diffuse
demyelinating polyradiculoneuropathy. Multifocal demyelination affects some neurons more than others,
resulting in prolonged and irregular CMAPs. Conduction velocities less than 70% of the lower limits of
normal are also diagnostic of demyelination. DL, distal latency; PL, proximal latency; CMAP, compound
muscle action potential.

particularly in the inflammatory myopathies, perhaps as a re-
sult of functional denervation caused by muscle fiber damage.
If the patient is cooperative or happens to activate the mus-
cle during the needle EMG study, additional information can
be obtained by observing MUP activity. MUP morphology is
diagnostic value: high-amplitude, long-duration motor unit
potentials indicate denervation with reinnervation, and low-
amplitude, polyphasic motor unit potentials suggest primary
disease of muscle or neuromuscular junction. Observation of
motor unit recruitment with increasing effort can be diagnostic
denervation in the absence of any other abnormality. With
derervation, MUP firing frequency increases with increasing ef-
sert, but insufficient numbers of different MUPs are recruited.
Conversely, rapid recruitment of small polyphasic MUPs sug-
gests myopathy or a disorder of neuromuscular transmission.

Increased variability of the shape of a single MUP suggests a
disorder of neuromuscular transmission.

Repetitive Stimulation
Disorders of neuromuscular transmission may be postsynap-
tic, as is the case in myasthenia gravis or most pharmacologic
neuromuscular blocking agents, or presynaptic, as in Lambert-
Eaton myasthenic syndrome and with exposure to botulinum
toxin. Repetitive supramaximal stimulation of a motor nerve
at a constant rate for five to ten stimuli is a simple way to as-
sess for deficits of neuromuscular transmission. The resultant
CMAP amplitudes should be constant. Progressive decrements
in amplitude across the first four to five responses with 3-Hz
stimulation is seen in both postsynaptic and presynaptic disor-
ders of neuromuscular transmission (Fig. 149.3). Progressive
increments in response at rates of stimulation above 20 Hz suggest a presynaptic neuromuscular block, as in Lambert-Eaton myasthenic syndrome, or botulism. An alternative—and more tolerable—means to look for this incremental response is to stimulate the nerve supramaximally just before and just after 10 to 60 seconds of sustained voluntary contraction of the muscle being tested. An increase in amplitude after exercise—postexercise facilitation—is seen in pre- and postsynaptic disorders; however, increases greater than 100% are seen only in presynaptic disorders (13). Repetitive stimulation is important in documenting residual neuromuscular blockade as a cause of weakness in ICU patients.

Electrodiagnostic studies are valuable extensions of the neurologic assessment, and need to be planned and interpreted in the context of the history and neurologic examination. For example, in some contexts, absent sensory nerve responses provide evidence that weakness is related to an acute disorder of nerve, but in other circumstances may reflect prior sensory neuropathy, focal entrapment, or technical difficulties when recording very small potentials in an electrically noisy environment. Well-trained technicians can perform routine nerve conduction and repetitive stimulation studies; however, needle EMG must be performed by a knowledgeable physician, and study planning and interpretation must be the responsibility of physicians expert in both clinical neurophysiology and the clinical assessment of neuromuscular disorders.

**Neuromuscular Disorders Requiring Intensive Care**

Table 149.3 lists some of the neuromuscular conditions that can cause respiratory failure. In many of these conditions, weakness develops gradually, and management does not require intensive care, except when intercurrent illness, such as aspiration pneumonia, causes decompensation. ALS inevitably leads to respiratory failure, but alternative arrangements for care usually preclude intensive care admission. In a minority of patients with ALS, however, respiratory insufficiency is the presenting symptom, and leads to intensive care admission before the diagnosis is made. The diagnosis is suggested by finding fasciculations, atrophy, weakness, and hyperactive reflexes in the absence of sensory loss, extrasynaptic muscle weakness, or autonomic dysfunction, and by excluding alternative causes, such as spinal cord compression or neuropathy. Electrophysiologic studies can be helpful. Nerve conduction studies document normal sensory nerve action potentials, and needle EMG reveals denervation in muscle of three or more extremes, or two extremities and bulbar muscles. Needle EMG can also document diaphragm denervation. Early in the course, clinical and electrophysiologic findings may not suffice for definitive diagnosis. Respiratory weakness is seen in some muscle disorders, and is a terminal event in Duchenne muscular dystrophy. Respiratory weakness can be the presenting feature of adult-onset acid maltase deficiency, a glycogen storage disease (19), and it is a feature of some of the congenital myopathies and muscular dystrophies. Respiratory weakness can occur in inflammatory myopathies in the context of severe proximal limb weakness, and polymyositis associated with Jo-1 antibodies can be associated with interstitial pulmonary disease (20).

The two neuromuscular disorders that most commonly lead to admission for intensive care are Guillain-Barré syndrome...
and myasthenia gravis. They are both autoimmune disorders and can cause rapidly progressive weakness; they are both treatable and, with appropriate management, most affected patients recover.

### Guillain-Barré Syndrome

**History.** In 1859, Landry (21) described ascending paralysis progressing to respiratory paralysis and death. Guillain, Barré, and Strohl described the classic features of progressive weakness, sensory symptoms without signs, and loss of tendon reflexes, but their patients recovered. They also described increased cerebrospinal fluid protein without cells (albuminocytologic dissociation), a finding that helped to distinguish this disorder from poliomyelitis (22). An association with prior infection was established (23,24), and the concept that the disease was of autoimmune pathogenesis was supported by the development of an animal model—experimental allergic neuritis (EAN), which is considered to be a good experimental model for Guillain-Barré syndrome (49). EAN can be induced by injections of several myelin components, including myelin basic protein, peripheral myelin protein-22 (PMP-22), and myelin-associated glycoprotein (MAG) (47). No specific myelin antibodies have been identified in the pathogenesis of ADIP.

The pathology of ADIP consists of a multifocal inflammation of peripheral nerves, in which macrophages destroy the myelin sheaths (43–46). This response is mediated by activated Th cells (47). Direct binding of antibodies to Schwann cell membranes with subsequent complement-mediated destruction and secondary macrophage invasion may also play a role (48). Similar pathologic findings characterize experimental allergic neuritis (EAN), which is considered to be a good experimental model for Guillain-Barré syndrome (49). EAN can be initiated by injections of several myelin components, including myelin proteins P0 and P2, myelin basic protein, peripheral myelin protein-22 (PMP-22), and myelin-associated glycoprotein (MAG) (47). No specific myelin antibodies have been identified in the pathogenesis of ADIP.

**Definition and Subtypes.** Guillain-Barré syndrome is an autoimmune disorder of peripheral nerves with progression over less than 4 weeks, which is manifested by weakness, reduced or absent tendon reflexes, and variable sensory and autonomic dysfunction (26). Subtypes have been distinguished based on the presence or absence of motor, sensory, and/or autonomic involvement, and on whether the predominant damage is to myelin sheaths or axons. Acute inflammatory demyelinating polyradiculoneuropathy (ADIP) is by far the most common subtype, accounting for more than 85% of cases in the United States (27). Patients have weakness and reflex loss, with varying degrees of sensory and autonomic involvement, and there is electrophysiologic and pathologic evidence of peripheral nerve demyelination. Patients who have no sensory loss and electrodiagnostic studies suggesting axonal rather than demyelinating pathology have acute motor axonal neuropathy (AMAN). This variety of Guillain-Barré syndrome was first described in Asia, where it occurs epidemically following gastroenteritis caused by Campylobacter jejuni (28). Acute motor sensory axonal neuropathy (AMSAN) is diagnosed when there is both motor and sensory involvement and nerve conduction studies are consistent with early axonal dysfunction (29). The axonal forms of Guillain-Barré comprise less than 5% of cases in Europe and North America, but up to 47% of cases in China, Japan, and Central and South America (30). Acute pandysautonomia (31,32) and some forms of acute sensory neuropathy (33) are sometimes considered to be subtypes of Guillain-Barré syndrome even though weakness is not a feature, since they run a similar time course, and are presumed to be autoimmune. The Miller-Fisher variant of Guillain-Barré syndrome features ophthalmoplegia, ataxia, and areflexia (34). The Miller-Fisher variant may overlap with other forms of Guillain-Barré syndrome (30,35).

### Epidemiology and Pathogenesis of Guillain-Barré Syndrome

The incidence of Guillain-Barré is less than 1 in 100,000 in children, averages 1 to 2 per 100,000 in adults, and increases to 4 in 100,000 in adults over 75 years of age (36,37). In about two thirds of patients, the disease follows an infection, most often a flulike syndrome or gastroenteritis, by 1 to 8 weeks (38). When serologic studies are performed, evidence of infection with C. jejuni, cytomegalovirus, Epstein-Barr virus, Haemophilus influenzae, and Mycoplasma pneumoniae are found to account for the majority of cases (39,40); 5% follow surgery (24). Although 1% of cases are attributed to vaccination (38), only rabies vaccine is associated with a definite increase in the incidence of Guillain-Barré (41); influenza vaccination causes little, if any, increase (41,42).

The pathology of ADIP consists of a multifocal inflammation of peripheral nerves, in which macrophages destroy the myelin sheaths (43–46). This response is mediated by activated Th cells (47). Direct binding of antibodies to Schwann cell membranes with subsequent complement-mediated destruction and secondary macrophage invasion may also play a role (48). Similar pathologic findings characterize experimental allergic neuritis (EAN), which is considered to be a good experimental model for Guillain-Barré syndrome (49). EAN can be initiated by injections of several myelin components, including myelin proteins P0 and P2, myelin basic protein, peripheral myelin protein-22 (PMP-22), and myelin-associated glycoprotein (MAG) (47). No specific myelin antibodies have been identified in the pathogenesis of ADIP.

The pathology of AMAN differs from that of ADIP in that macrophages target the axonal membrane in ventral (motor) roots and nerves at nodes of Ranvier, resulting in axonal rather than myelin damage (50,51). The pathology in AMSAN is similar to that of AMAN, except that the disorder affects both motor and sensory roots and nerves (29). Recent evidence suggests that AMAN may result from molecular mimicry. The capsule of the strains of C. jejuni implicated in patients with Guillain-Barré syndrome contains a lipopolysaccharide with a structure similar to the GM1 ganglioside present in Table 149.3

<table>
<thead>
<tr>
<th>NEUROMUSCULAR CAUSES OF RESPIRATORY FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISORDERS OF NERVE</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Toxic neuropathies</td>
</tr>
<tr>
<td>Critical illness polyneuropathy</td>
</tr>
<tr>
<td>Phrenic neuropathy (brachial plexus neuropathy, radiation trauma)</td>
</tr>
<tr>
<td>DISORDERS OF NEUROMUSCULAR JUNCTION</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Acetylcholine receptor antibody associated</td>
</tr>
<tr>
<td>Muscle-specific kinase (MuSK) antibody associated</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
</tr>
<tr>
<td>Botulism</td>
</tr>
<tr>
<td>Pharmacologic neuromuscular blockade</td>
</tr>
<tr>
<td>DISORDERS OF MUSCLE</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
</tr>
<tr>
<td>Muscular dystrophies (dystrophinopathies, limb girdle types 2A and 2L, myotonic muscular dystrophy, myobiblar myopathy)</td>
</tr>
<tr>
<td>Congenital myopathies (neonatal rod, centronuclear)</td>
</tr>
<tr>
<td>Glycogen storage disorders (acid maltase deficiency, debrancher enzyme deficiency)</td>
</tr>
<tr>
<td>Other inherited myopathies (mitochondrial myopathies, distal muscular dystrophy with respiratory weakness)</td>
</tr>
<tr>
<td>Metabolic myopathies</td>
</tr>
</tbody>
</table>

The capsule of the strains of C. jejuni implicated in patients with Guillain-Barré syndrome contains a lipopolysaccharide with a structure similar to the GM1 ganglioside present in patients with Guillain-Barré syndrome.
Peripheral nerves. Antibodies to these strains of C. jejuni cross-react with peripheral nerve GM1 ganglioside, resulting in axonal dysfunction in experimental animals (52). Similarly, many patients with the Miller-Fisher variant have GQ1b and GT1a antibodies (53) that cross-react with Campylobacter lipopolysaccharides (54-55). Anti-GQ1b antibodies have been associated with acute and chronic sensory neuropathies (30). Although there is evidence that molecular mimicry is a plausible explanation for some patients with Guillain-Barré polyneuropathy, the relationships are complex. Patients may have antibodies to several gangliosides, antibodies to a particular ganglioside can be associated with several different types of neuropathy, and infections with a specific organism may be followed by more than one kind of neuropathy (30).

Clinical Presentation and Diagnosis. AIDP, the most common form of Guillain-Barré, presents with weakness and decreased or absent tendon reflexes. It is a non-length-dependent polyneuropathy, with proximal as well as distal weakness that usually begins in the legs and ascends, but can affect other regions first. Bilateral facial weakness occurs in half of the patients. Since symptoms can progress to oropharyngeal and respiratory weakness in 33% of patients, all patients require careful monitoring, as discussed below. Eye movements are usually spared, the exception being the Miller-Fisher variant. Sensory symptoms occur in 80% of patients. Sensory signs are less frequent and often mild, but, when prominent, can contribute significantly to disability (56). Pain and temperature sensation mediated by small unmyelinated neurons may be affected less than position and vibratory sensation, mediated by large myelinated fibers. Fifty percent have pain, either back and muscle pain that can be aggravated by movement, or neuropathic pain, such as burning paresthesias, sometimes with allodynia (pathologic sensitivity to touch). Tendon reflexes are lost early in the course of the disease; indeed, the diagnosis should be questioned if reflexes are retained. Autonomic dysfunction is present in 66% of patients, and can manifest with tachycardia or bradycardia, spontaneous or orthostatic hypotension, paroxysmal hypertension, abnormalities of sweating, urinary retention, or ileus (57). Guillain-Barré syndrome is a subacute process: 50% of patients stop progressing in less than 2 weeks, 80% by 3 weeks, and more than 90% by 4 weeks (58).

The much less common axonal variants of Guillain-Barré are distinguished from AIDP by electrophysiologic studies. Nerve conduction studies should show low-amplitude motor (CMAPs) without marked conduction slowing, conduction block, or dispersion in both AMAN and AMSAN. AMAN is distinguished from AMSAN by preservation of sensory nerve action potentials amplitudes (59).

The differential diagnosis of patients presenting with subacute weakness includes disorders of the CNS, PNS, neuromuscular junction, and muscle. Although Babinski responses, brisk reflexes, and sensory level will usually distinguish spinal cord from peripheral nerve diseases, there is overlap because reflexes may be depressed acutely in CNS disorders; bladder dysfunction, while suggestive of CNS lesions, can be seen in Guillain-Barré; and CNS demyelination may occasionally accompany Guillain-Barré syndrome (60). Conversely, Guillain-Barré syndrome should be in the differential of patients with the locked-in syndrome when tendon reflexes are depressed. Toxic, drug-induced, and metabolic neuropathies may occasionally present over a similar time course as Guillain-Barré syndrome. In patients without sensory disturbances, disorders of neuromuscular junction and muscle should be considered. Muscle disorders that can present with severe subacute or acute weakness include the periodic paralyses, hypokalemic myopathy, drug-induced myopathies, and inflammatory myopathies.

Evaluation should include appropriate imaging to exclude CNS disorders, routine laboratory studies, and lumbar puncture. The cerebrospinal fluid (CSF) is normal during the first days of illness, after which there is a transient elevation of protein with minimal or no pleocytosis. A significant pleocytosis should raise the question of infection such as Lyme disease or West Nile virus (61); when the clinical picture is otherwise classic for Guillain-Barré, CSF pleocytosis should suggest human immunodeficiency virus (HIV) infection in which immune dysregulation increases the incidence of autoimmune disorders (62). Blood should be sent for basic metabolic profile, B12, porphyrins, tests for Lyme disease and HIV, and heavy metal levels. Electrodiagnostic studies must be interpreted in the context of the clinical findings. Early in Guillain-Barré, nerve conduction and F-wave studies may be normal if recorded from a limb without severe weakness. Delayed or absent F waves, sometimes replaced by axon reflex waves, are the earliest abnormalities (63). When recorded from a paralyzed muscle, normal motor nerve conduction studies with normal F waves indicate that the weakness does not result from a peripheral cause, and should direct attention toward an alternative diagnosis with localization to the central nervous system.

Management of Guillain-Barré Syndrome. Patients with Guillain-Barré syndrome should be transferred to the ICU. Respiratory failure is often preceded by progression of weakness to involve the upper extremities, shoulders, neck, and face, but may occur before this weakness is evident. Tachypnea, paradoxical respirations, hypophonia,
The neuromuscular junction is composed of a presynaptic motor neuron membrane, the synaptic cleft, and the postsynaptic muscle membrane. In the normal neuromuscular junction, the arrival of an action potential at the nerve terminal leads to the influx of calcium through voltage-gated calcium channels, which triggers release of acetylcholine into the synaptic cleft (87). Acetylcholine diffuses across the synaptic cleft to bind with acetylcholine receptors on the postsynaptic muscle membrane. This binding generates end-plate potentials that depolarize the muscle membrane. When the depolarization exceeds threshold, a muscle action potential is generated, which leads to a cascade of events that results in muscle contraction (88). Neuromuscular transmission fails if the end-plate potential fails to reach the threshold for muscle action potential generation. In Lambert-Eaton myasthenic syndrome, the end-plate potential is small because antibodies to voltage-gated calcium channels on the presynaptic membrane interfere with acetylcholine release. In myasthenia gravis, the end-plate potential is small because antibodies to the acetylcholine receptor receptor or related sites on the postsynaptic membrane decrease the depolarization caused by normal amounts of acetylcholine.

The acetylcholine receptor is composed of four subunits (89). Antibodies to the acetylcholine receptor can be found in 80% to 90% of patients with generalized myasthenia (90). These antibodies can cause neuromuscular transmission failure by binding to the acetylcholine receptor and altering function, by increasing the rate of degradation of the receptors, and by complement-mediated destruction of the postsynaptic membrane (91). About 30% of patients with generalized myasthenia who are seronegative for acetylcholine receptor antibodies have antibodies to muscle-specific kinase (MuSK) (92). Patients with MuSK antibodies demonstrate more severe disease than patients with antibodies to acetylcholine receptor (93).

The thymus gland has been implicated in the pathogenesis of myasthenia gravis. Thymic abnormalities are seen in 75% of patients with myasthenia gravis. Of these, 75% have lymphoid follicular hyperplasia and 15% have thymomas (94). Acetylcholine receptors are found on myoid cells of the thymus (95). The majority of myasthenic thymuses contain B cells that can produce antibodies to the acetylcholine receptor (96). Anti-striated muscle antibodies in patients with myasthenia gravis correlate highly with thymoma (97). Patients with myasthenia gravis often have other autoimmune disorders, including thyroiditis, scleroderma, Sjogren syndrome, rheumatoid arthritis, pernicious anemia, polymyositis, and lupus erythematosus (98).

**Clinical Presentation.** Patients with myasthenia gravis present with fluctuating weakness that improves with rest. The most common complaints are ocular—namely, ptosis and diplopia related to weakness of the levator palpebrae and the extraocular muscles, respectively. Prolonged or repeated activity in 50% to 90% of patients, and 90% to 95% of patients complain of diplopia during the disease. Weakness can remain purely ocular in up to 15% of cases, but the majority of patients with myasthenia gravis develop generalized symptoms (76). Dysarthria and dysphagia are common complaints. Neck extension or extension of the neck is more involved than other muscles in generalized disease (76). Patients may have to support their chin with their hands to prevent head drop because of neck extensor weakness or to keep their jaw shut because of weakness of the temporalis and masseter muscles. Proximal limb weakness is usually present when the disease is not purely ocular. It is sometimes asymmetric, is occasionally very focal, and...
MYASTHENIC WEAKNESS

TABLE 149.4

<table>
<thead>
<tr>
<th>DRUGS THAT COMMONLY WORSEN MYASTHENIC WEAKNESS</th>
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</thead>
<tbody>
<tr>
<td>Neuronal blocking agents</td>
</tr>
<tr>
<td>Aminoglycoside antibiotics (gentamicin, neomycin, tobramycin, kanamycin, and others)</td>
</tr>
<tr>
<td>Procainamide, quinidine, quinine</td>
</tr>
<tr>
<td>Penicillamine*</td>
</tr>
<tr>
<td>α-Interferon*</td>
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<td>Magnesium salts</td>
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<thead>
<tr>
<th>DRUGS THAT MAY WORSEN MYASTHENIC WEAKNESS (SELECTIVE LIST)</th>
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<tbody>
<tr>
<td>Macrolide antibiotics (erythromycin, azithromycin, and others)</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Anticonvulsants (Dilantin, gabapentin, carbamazepine, and others)</td>
</tr>
<tr>
<td>Narcotic analogues</td>
</tr>
<tr>
<td>Estrogen therapy</td>
</tr>
<tr>
<td>Timolol, betaxalol hydrochloride (ophthalmic solutions)</td>
</tr>
<tr>
<td>Phentothiazine</td>
</tr>
<tr>
<td>Chloroquine</td>
</tr>
<tr>
<td>Iodinated contrast agents</td>
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</table>

*May cause autoimmune myasthenia gravis.


myasthenia presents with proximal weakness without bulbar or ocular weakness.

Myasthenic crisis is diagnosed when weakness progresses to cause dysphagia with loss of airway protection or hypventilation. Myasthenic crisis can be precipitated by infection, surgical procedures, pregnancy, treatment with corticosteroids, sepsis, cholinergic crisis, and the rapid withdrawal of immune-suppressing medications (86). Pulmonary system infection, including aspiration pneumonia, is the most common identifiable precipitating factor (86). Many medications can also worsen myasthenic symptoms (Table 149.4) (99), often because they impair neuromuscular transmission. Aminoglycoside antibiotics, quinidine, and procainamide are particularly likely to cause weakness, and should be avoided in patients with myasthenia. Limited experience with telithromycin suggests that it should also be avoided (100). Penicillamine and α-interferon may cause autoimmune myasthenia. Evidence that other medications exacerbate myasthenia gravis is less convincing, but in patients with increasing weakness, all medications must be scrutinized against the long list of potentially offending agents (99).

Myasthenic crisis can involve muscles of inspiration, including the diaphragm and the external intercostals, along with accessory muscles of inspiration, including the scalene and sternocleidomastoid muscles. Respiratory strength can be measured by vital capacity and negative inspiratory force (101). As respiratory weakness leads to ventilatory failure, tidal volumes decline. Patients in myasthenic crisis have an intact respiratory drive, and therefore respond to the decrease in tidal volume with an increase in respiratory rate (102). Oropharyngeal muscle weakness may result in obstruction with upper airway collapse. Secretions can be difficult to control and can also obstruct the airway and lead to asphyxiation. In the 1950s and 1960s, mortality from myasthenic crisis was as high as 70% to 80% (103,104). In more recent reports, mortality is closer to 4% (85,86), related to improvements in intensive care as well as effective immunomodulatory treatment.

Diagnosis. The history and examination often strongly suggest the diagnosis. A history of fluctuating ptosis, diplopia, fatigable dysarthria, dysphagia, and neck weakness are highly suggestive. Sometimes the presentation may be misleading, as when oculary myasthenia presents with isolated eye muscle weakness or with a pattern of eye movements that mimics internuclear ophthalmoplegia from brainstem lesions, or when patients have proximal limb weakness without eye or bulbar weakness, suggesting a primary disorder of muscle. Conversely, patients with purely ocular findings should be worked up for other causes of ophthalmoplegia, including thyroid eye disease and retrobulbar or cavernous sinus lesions. ALS may present with bulbar symptoms, but patients with ALS do not have ptosis or eye movement weakness, and often have pseudobulbar dysarthria, characterized by slow labored speech and poorly modulated emotional expression, with laughing or crying that is disproportionate to the situation.

Many tests are available to confirm the diagnosis of myasthenia. Definitive diagnosis is important, as most patients will require years of immunomodulatory therapy. Pharmacologic testing with edrophonium (Tensilon), a rapid-acting, short duration acetylcholinesterase, can result in transient increase in strength. Caution should be used in using edrophonium because anticholinergic side effects, such as bradycardia and bronchospasm, can develop. A test dose of 2 mg of edrophonium, given intravenously, should be administered, followed by increments of 2 mg, for a total dose of 10 mg. Atropine should be available to counteract muscarinic side effects (105). Definite improvement in strength, as demonstrated by improvement in ptosis, dysarthria, or resistance against the examiner’s testing, is supportive of the diagnosis. The test is, therefore, most helpful in patients with clear weakness that can be evaluated in an objective manner (105). In patients with cardiac disease, especially those on β-blockers or drugs that cause atrioventricular block, edrophonium should be avoided, as it can cause asystole (106). Fortunately, there are many alternative tests to confirm the diagnosis of myasthenia.

Serum acetylcholine receptor antibodies are found in 80% to 90% of patients with generalized myasthenia gravis, and have very high diagnostic specificity. Increased titers are also found in patients with thymoma without myasthenia, and rarely in other diseases, including systemic lupus, ALS, liver disease, and inflammatory neuropathies, and in patients with Lambert-Eaton myasthenic syndrome (107). Antibodies to striated muscle are present in about 30% of patients with myasthenia gravis, and are highly associated with thymoma (108). About 30% of patients with myasthenia gravis who lack antibodies to acetylcholine receptor have antibodies to MuSK. Other antibodies directed against muscle antigens can be found in patients with myasthenia gravis (109).

Repetitive nerve stimulation can be performed to rule out a decrement in the amplitude or area of the fourth or fifth
Myasthenic crisis is common in patients ineffective cough, or vital capacities less than 20 to 25 mL/kg bulbar weakness who have difficulty controlling secretions, an hospitalized for definitive management. Patients with progressive patients with worsening myasthenic symptoms should be hospitalized prior to treatment with steroids. Management. The majority of myasthenic patients respond well to treatment and never require intensive care. Although anticholinesterase medications can produce dramatic improve- ment in strength, they do not address the underlying autoim- mune pathogenesis of the disease, and tend to become ineffec- tive as the disease progresses. They may be sufficient, however, for some patients with myasthenia gravis as the disease advances. They may be helpful as adjunctive treatment in patients on immunosup- pressant therapy. Pyridostigmine, which does not cross the blood-brain barrier, is the most commonly used oral agent. Sustained-release pyridostigmine is appropriate for use at bed- time to mitigate weakness during the night and in the morning; however, multiple daytime doses of sustained-release prepara- tions should be avoided, as accumulation may lead to cholin- ergic weakness.

Oral prednisone is the most commonly used agent to induce remission in myasthenic patients, and is effective in 80% to 90% of patients. High-dose prednisone—60 to 100 mg/day— may cause transient worsening of myasthenia, and should not be initiated unless patients can be closely observed. Lower doses appear safer, but are not entirely free from this com- plication. Most patients experience gradual improvement in strength beginning 2 or 3 weeks after initiation of therapy. Once a good response has been achieved, the dose can be tapered over several months to low-dose alternate-day treatment. Doses less than 40 mg every other day are generally well tolerated. Doses of 40 mg or above every other day are associated with many long-term side effects, including diabetes, hypertension, cataracts, avascular necrosis, and increased susceptibility to infection. Azathioprine may reduce steroid dependence. Treat- ment with IVIG can produce rapid improvement in strength, and may be useful to provide short-term improvement while waiting for steroids to become effective.

Myasthenic weakness can progress very rapidly; therefore, patients with worsening myasthenic symptoms should be hos- pitalized for definitive management. Patients with progressive bulbar weakness who have difficulty controlling secretions, an ineffective cough, or vital capacities less than 20 to 25 mL/kg should be admitted to the ICU (112,113). When the vital ca- pacity reaches 15 mL/kg, endotracheal intubation should be strongly considered. Effective intubation can be predicted by abrupt respiratory failure and mucous plugging (114). Inter- mittent mandatory ventilation with pressure support is used to reduce alveolar collapse or atelectasis. Positive end-expiratory pressure can reduce complications related to atelectasis (115). If mechanical ventilation is required for more than 2 weeks, tracheostomy should be considered. The most common complica- tions of myasthenic crisis are fever, pneumonia, and at- electasis (86). Aggressive respiratory treatment with suction- ing, bronchodilator treatments, sighs, chest physiotherapy, and intermittent positive pressure can reduce the complications of mechanical ventilation and shorten the period that patients are in the intensive care unit (116). Weaning trials should be at- tempted with patients who show clear improvement of respir- atory muscle strength, with the goal to eliminate mandatory ventilation and then reduce the amount of pressure support. Cholinesterase inhibitors are generally discontinued after intuba- tion because of increased secretions and the potential for depolarization blockade. After a definitive response to treatment, cholinesterase inhibitors can be restarted at a low dose.

Plasma exchange has been shown to be effective for the treatment of myasthenic crisis and to prepare patients for surgery (117). Many different protocols are used, but a se- ries of five to six exchanges of 2 to 4 liters every other day is most commonly employed. Improvement can usually be seen in 3 to 4 days and can last for several weeks, but is not sus- tained without the addition of an immune suppressant agent. Side effects of plasma exchange, which can be life threatening, include hypotension, bradycardia, congestive heart failure, thrombotic thrombocytopenic purpura, nosocomial thrombosis, infection, and dramatic shifts in electrolytes, including calcium. Controlled randomized trials have demon- strated that IVIG is as effective as plasma exchange in patients with myasthenic crises (118). This trial used 1.2 and 2.0 g/kg of IVIG over 2 to 5 days. Patients who fail to respond to IVIG may subsequently respond to plasma exchange (119). Intrave- nous steroids have been used in high doses in myasthenic crisis in patients who do not respond to IVIG or plasma ex- change (120), but this may be complicated by transient wors- ening of myasthenic weakness that may precipitate the need for, or prolong, mechanical ventilation. Other immune-suppressant medications can be useful as steroid-sparing drugs and as sole therapy for myasthenia, but they take weeks or months to pro- duce improvement, and therefore are not appropriate choices to treat myasthenic crisis.

Thymectomy is indicated in patients with thymoma, and is also accepted therapy for myasthenia gravis without thy- moma, particularly in younger patients without thymic invo- lution. However, the absence of class I evidence and the short- comings of existing case-control or cohort trials have led to a call for prospective randomized controlled clinical trials (121).

Perioperative Care. Myasthenic crisis is common in patients undergoing surgical procedures. The main risk factors for postoperative complications include severe bulbar weakness, chronic myasthenia, respiratory illness, and decreased vital ca- pacity preoperatively (122). Whenever possible, preoperative treatment to improve strength should be undertaken. Plasma exchange or IVIG can be performed preoperatively in patients with bulbar weakness or generalized myasthenia. A response is often seen within 3 to 6 days, although preoperative IVIG has
shown a variable time to maximal response (123). Preoperative pulmonary function testing can be performed to assess respiratory function. Drugs that are known to exacerbate myasthenia (Table 149.4) should be avoided whenever possible.

**Critical Illness Polyneuropathy and Myopathy**

**History.** Although earlier references are cited [see Lindsay et al. (124,125)], recognition that critically ill patients frequently develop new neuromuscular dysfunction was not widespread until the last decade of the 20th century. In 1984, Bolton et al. (126) described five patients who failed to wean from the ventilator after treatment of sepsis, and were found to have neuromuscular weakness related to an axonal sensorimotor polyneuropathy. They called this critical illness polyneuropathy (CIP). In 1992, Sagredo et al. (127) attributed prolonged paralysis, seen in patients in whom vecuronium had been weaned, to persistent plasma levels of vecuronium metabolites in those patients with impaired renal function. Hirano et al. (128) described severe weakness in two critically ill asthmatic patients treated with steroids and nondepolarizing blocking agents. Muscle biopsy demonstrated depletion of thick myosin filaments. They called this acute myopathic polyneuropathy. Other terms for the same or similar illness have included hydrocortisone myopathy, necrotizing myopathy, thick filament myopathy, postparalysis syndrome, and acute myopathy of intensive care; we will refer to it by the most common designation: critical illness myopathy (CIM). The term critical illness neuromyopathy (CINM) is used to refer to patients in whom both neuropathy and myopathy coexist, or when it is uncertain which condition is causing the patient’s weakness. The term CINM could also be applied to patients with persistent neuromuscular blockade; however, electrophysiologic studies should exclude this as a contributing factor in most patients.

**Epidemiology.** The incidence of critical illness neuromyopathy is estimated to be as high as 70% of mechanically ventilated ICU patients with sepsis and multiorgan failure. Witt et al. (129) found, in a prospective study, that 70% of 43 ICU patients with sepsis and failure of more than two organs developed electrophysiologic evidence of peripheral neuropathy, and half of these patients had clinically evident neuropathy with difficulty being weaned from the ventilator. De Jonghe et al. (130) found that 25.3% of ICU patients intubated for 7 or more days developed neuromuscular weakness. All had sensorimotor axonopathy, and all who were biopsied also had myopathy. Bednarik et al. (131) prospectively studied 61 ICU patients with evidence of multiorgan failure; 27% had clinical and 54% electrophysiologic evidence for critical illness neuromyopathy. Bercker et al. (132) found that 60% of 50 consecutive patients with acute respiratory distress syndrome studied retrospectively developed critical illness neuromyopathy.

**Pathophysiology**

**Critical Illness Polyneuropathy.** Sepsis and multiorgan failure are the major risk factors for CIP (133,133,134); other risk factors include duration of mechanical ventilation, hyperglycemia, hyperosmolality, and decreased serum albumin (129). The peripheral nervous system is one of the organ systems damaged in systemic inflammatory response syndrome (SIRS). Decreased capillary flow and increased capillary permeability related to sepsis-related cytokine release, and other factors such as a generally high catabolic rate, result in a reduced supply of nutrients, decreased clearance of toxic factors (including medications), and tissue edema. Pathologically, there is axonal degeneration without inflammation, and there is an increase in adhesion molecule expression in nerve (113).

**Critical Illness Myopathy.** Risk factors for CIM overlap with those for CIP; however, there is more emphasis on primary pulmonary disease (asthma and acute respiratory distress syndrome [ARDS]) and on the use of neuromuscular blocking agents and corticosteroids (130,135). Apoptotic activity may be increased. High corticosteroid levels may increase expression of ubiquitin, leading to increased proteolytic activity (136). Denervation from coexisting CIP may also make the muscle more susceptible. Muscle biopsy shows loss of thick (myosin) filaments; there may also be fiber-type atrophy and/or necrosis (128,137). Whether the different pathologies represent a spectrum of severity or different entities remains unsettled. Most patients on ventilators are given neuromuscular blocking agents. Normally, the effects of these agents wear off within hours of discontinuation; however, it is not unusual for residual blockade to last 1 to 2 days (127). Early reports of more prolonged weakness after neuromuscular blockade did not consider the effects of CIP and CIM. In a recent review, Murray et al. (135) concluded that nondepolarizing neuromuscular blocking agents may potentiate muscle weakness by a number of mechanisms, including up-regulation of acetylcholine receptors with fetal-type receptors that are less responsive to acetylcholine, presynaptic inhibition of exocytosis of acetylcholine, and potentiation of muscle damage by corticosteroids and by sepsis-induced ischemia.

**Clinical Presentation.** CIP is preceded by sepsis and failure of more than one organ. Sepsis leads to SIRS, which is manifested by two or more of the following (138):

- Elevated (greater than 38°C) or reduced (less than 36°C) temperature
- Tachycardia (greater than 90 beats/minute)
- Tachypnea (greater than 20 breaths/minute)
- Temperature less than 32 mm Hg
- High (greater than 12,000) or low (less than 4,000 cells/μL) white blood cell count

Most patients have a septic encephalopathy manifested by confusion and reduced responsiveness, and most require ventilatory assistance. With antibiotic treatment, sepsis and septic encephalopathy improve, and patients awaken, tracking the examiner with the eyes and demonstrating comprehension with eye movements or weak limb movements; in patients who cannot cooperate for the examination, weakness is manifested by decreased or absent spontaneous limb movement and difficulty weaning from the ventilator. The diagnosis of CIP is further supported if reflexes are absent and if a sensory loss can be demonstrated; however, not all patients with CIP have absent reflexes or sensory loss on examination, and, in many patients, an accurate sensory examination cannot be done. Electrodiagnostic studies are, therefore, key to diagnosis. CIM may have similar antecedents, but is more likely in the setting of ventilatory failure from asthma (128,137) or ARDS (132). The use of neuromuscular blocking agents (139) and corticosteroids (130) appears to predispose to CIM, although CIM has been reported without either one (140). Clinically, the presentation is similar to that of CIP. Sensation is normal if
neuropathy does not coexist, but often confusion and poor communication make it difficult to assess sensation. Here again, electrophysiologic testing is key to diagnosis.

Diagnosis. Critical illness neuromyopathy should be suspected in any critically ill patient whose medical condition is improving but who appears to have trouble moving or cannot be weaned from the ventilator. A diagnostic algorithm is presented in Figure 149.4. The diagnosis is likely in patients with risk factors, particularly sepsis, SIRS, major organ failure, prolonged artificial ventilation, hyperglycemia, and exposure to neuromuscular blocking agents or corticosteroids (141). Alternative causes for weakness in the ICU must be considered and, if possible, excluded. These include medications that cause myopathy, neuromuscular blockade, or neuropathy; electrolyte disorders such as hypokalemia or hypophosphatemia; undiagnosed neuromuscular disorders such as myasthenia gravis, Guillain-Barré syndrome, or ALS; and a variety of central nervous system disorders, including ischemic myelopathy, anterior horn cell loss from hypoxia (142), central pontine myelolysis that most often follows rapid correction of hyponatremia (143), and hemispheric stroke from hypotension, embol, or hemorrhage (144). West Nile encephalitis (WNE) should be considered in patients who present with fever and encephalopathy, and in those who develop neuromuscular weakness, since WNE can affect anterior horn cells and, less often, peripheral nerves (145). Depending on clinical suspicions, imaging of the brain and spinal cord may be appropriate. If clinical findings suggest neuromuscular weakness rather than a CNS disorder, it may be more efficient to confirm with electrophysiologic studies than to pursue studies for CNS disorders.

Laboratory studies should include a basic metabolic profile to assess blood sugar and electrolytes. Elevation of creatine kinase (CK) may suggest myopathy, and very high CK suggests rhabdomyolysis. Normal CK does not exclude critical illness myopathy, and mild elevations in CK can be seen with acute myoglobinuria. Tests for myasthenia (see above) are indicated when there is a clinical suspicion. Spinal fluid findings are not often reported in CIP. Lumbar puncture is indicated principally if there is clinical suspicion of infection.

Electrodiagnostic testing is helpful to confirm a neuromuscular disorder and to distinguish among disorders of nerve, neuromuscular junction, and muscle (for a more detailed synopsis, see Dhanda [146]). Repetitive nerve stimulation at 2 to 3 Hz will show a decremental response (Fig. 149.3) in patients with disorders of neuromuscular transmission. If the patient has been given neuromuscular blocking agents, repeat testing in 1 to 2 days should demonstrate resolution of neuromuscular blockade. Other causes of neuromuscular blockade should be considered if decremental responses persist. Motor nerve conduction studies will show a decreased amplitude CMAP in patients with CIP within several days of the onset of weakness (to allow for Wallerian degeneration). In patients with CIM, the CMAP is also of low amplitude, but may also be prolonged (147). Sensory nerve action potentials are often reduced or absent in CIP, and should be normal in CIM, unless there is coexistent CIP. It should be kept in mind that preexisting neuropathy may account for some of the deficits found on electrophysiologic testing, as, for example, in patients with diabetic neuropathy. Guillain-Barré polyneuropathy can follow surgery or trauma, and could therefore occur in settings similar to the critical illness neuromyopathies. Electrophysiologic findings diagnostic of demyelinating neuropathy—not found in CIP or CIM—would suggest this possibility, leading to a trial of IVIG or plasma exchange. In theory, an axonal form of Guillain-Barré would be electrophysiologically indistinguishable from CIP. This highly unlikely occurrence should be considered in patients who lack the usual risk factors for CIP. Needle EMG studies may show abnormal spontaneous activity in patients with neuropathy, but only after 2 to 3 weeks of denervation. Voluntary activity may be difficult to study in poorly cooperative patients; however, when the patient can take a full effort, there will be reduced recruitment in neuropathy and small polyphasic motor unit potentials in myopathy, helping to differentiate CIP from CIM.

Additional electrodiagnostic studies that may be useful in diagnosis include phrenic nerve stimulation, diaphragmatic EMG, and direct muscle stimulation. While these studies do not require specialized equipment, many electromyographers do not have sufficient experience with them to be confident in their performance or interpretation. Phrenic nerve stimulation in the neck with surface recording over the diaphragm shows a normal response in patients with pulmonary causes of respiratory failure, but a low amplitude or absent response in patients with neuromuscular respiratory weakness. Needle EMG of the diaphragm can be done in patients without severe chronic obstructive pulmonary disease (COPD), delir, or cough-apnea, and may diagnose denervation or myopathy affecting the diaphragm (148). CIP and CIM may be distinguished by comparing the muscle response to direct muscle stimulation with the response to nerve stimulation. If the response to muscle stimulation is larger than to nerve stimulation, CIP is likely; when both are small, CIM is likely (149,150).

In patients suspected of having CINM, nerve and muscle biopsy may document axonal neuropathy or myopathy with loss of myonem filaments; however, it may only change management if they demonstrate an alternative diagnosis that may be amenable to treatment, such as a demyelinating or vasculitic neuropathy, or an inflammatory myopathy. In patients whose neuromuscular deficits are clearly related to the usual risk factors for CINM, treatable conditions are not sufficiently likely to warrant biopsy (151).

Management. Of the factors that may contribute to the development of CINM, many—like the response to sepsis and the incidence of multiorgan failure—are related to the severity of the presenting critical illness, and are not easily modifiable. It remains to be demonstrated whether the reduced use of corticosteroids or neuromuscular blocking agents will result in a decreased incidence of CIM. It makes sense, however, to eliminate continued exposure to either type of agent whenever possible. It also makes sense to avoid medications that can be neurotoxic, or those that can interfere with neuromuscular transmission. Intensive insulin therapy in critically ill patients has been demonstrated to reduce the risk of CIP by 49% over standard therapy (152). The safety and efficacy of intensive insulin therapy remains controversial, however (153,154), and is currently the subject of several prospective controlled multicenter studies.

Patients with neuropathy will be more prone to pressure palsies, and thus, great care must be taken in positioning and support to avoid this complication. Physical therapy should be directed toward avoiding contractures until the patient is able to participate in strengthening exercises.
Section XIV: Neurologic Disease and Dysfunction

FIGURE 149.4. Algorithm for diagnostic evaluation and management of weakness developing in the intensive care setting. CIDP, chronic inflammatory demyelinating polyneuropathy; CIM, critical illness myopathy; CINM, critical illness neuromyopathy; CIP, critical illness polyneuropathy; CK, creatine kinase; CNS, central nervous system; GBS, Guillain-Barré syndrome; LEMS, Lambert-Eaton myasthenic syndrome; LP, lipid peroxidation; MG, myasthenia gravis; NM, neuromuscular.
Prognosis. There is no comprehensive study on prognosis in CINM. Mortality is high early in the course, and is related to the underlying critical illness (155). Patients with CINM who survive the acute illness and who begin to recover strength are likely to continue to recover over the weeks to months that follow; it is sufficient to monitor improvement with clinical assessment of strength. Patients with CINM who fail to show clinical improvement in strength can be evaluated with repeat electrophysiologic testing. Patients with electrophysiologic evidence of severe axonal loss, with small or absent responses to nerve stimulation and abundant positive waves and fibrillation potentials on EMG, are likely to have residual deficits—sometimes severe (129, 155–157). Although the test of regenerating severely damaged axons may be more accurate than regenerating motor units, it is not clear whether the prognosis for recovery from CINM is better than from CMP (158, 159).

**SUMMARY**

Neuromuscular diseases may necessitate admission for intensive care to provide airway protection and respiratory support. Disorders such as Guillain-Barré syndrome and myasthenia gravis can lead to precipitous weakness, and require careful monitoring so that assistance can be given before hypoxemia occurs. Management must also address autonomic dysfunction, sensory loss, pain, and psychological distress. Neuromuscular disorders of autonomic pathogenesis often respond to specific treatment, and a favorable outcome can be expected for many of the major patients. The critical illness neuromyopathies have become the most common cause of weakness that develop in the intensive care setting, requiring critical care physicians to be familiar with their presentation, diagnosis, and management. Although no specific treatment is available for CINM, most patients improve with supportive care. A minority, however, are left with irreversible weakness. Attempts to address the factors that predispose to CINM may eventually reduce the burden of this recently discovered group of neuromuscular disorders.

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