Neuromuscular Disorders and Acute Respiratory Failure: Diagnosis and Management

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KEYWORDS

• Neuromuscular • Respiratory failure • ALS • Myasthenia gravis • Guillain-Barré • CIDP • Critical illness myopathy

The diagnostic approach to a patient with respiratory failure starts with the determination of whether the respiratory failure is the result of a cardiopulmonary disease versus a primary neurologic disorder. The latter can occur in the setting of either a central nervous system (CNS) disease such as cervical myelopathy, lower brainstem injury, or diffuse bihemispheric involvement, or a neuromuscular disease (NMD). This review focuses on NMDs that result in respiratory impairment because of weakness of the respiratory muscles.

An NMD may result in respiratory weakness when there is impaired function of a large proportion of the motor units that innervate the respiratory muscles. A motor unit is referred to a motor neuron (located in the anterior horn cells of the spinal cord or the motor nuclei of the cranial nerves in the medulla and pons), its axon, and all the myofibers that it innervates (**Fig. 1**). Neuromuscular weakness may also result from diseases that primarily affect the myofiber plasma membrane or its contractile apparatus.[1]

PATHOPHYSIOLOGY

NMDs often present with acute or subacute respiratory weakness and a rapidly evolving respiratory failure. On the other hand, the more indolent NMDs may also

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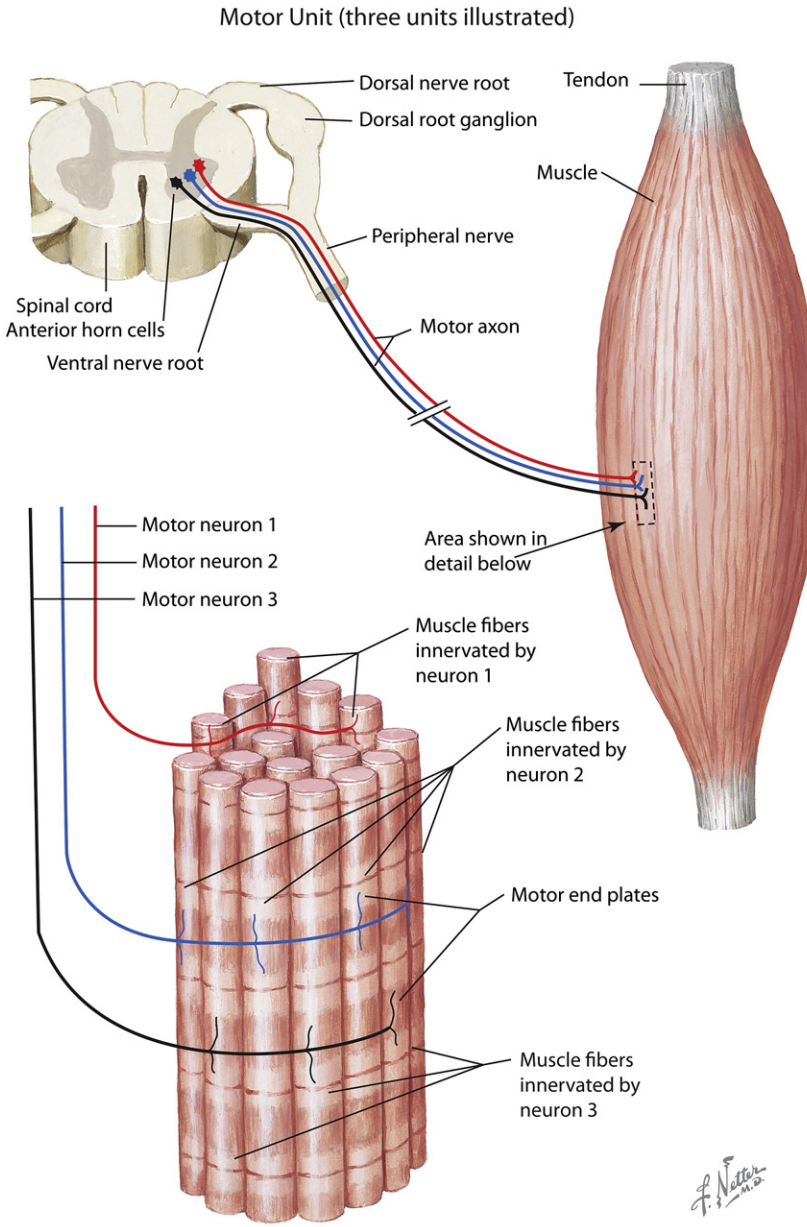

Fig. 1. A motor unit. (*Courtesy of* Netter Images; with permission.)

present with an acute respiratory failure, which could be the result of disease progression to a point that the compensatory mechanisms are overwhelmed, or emergence of a superimposed respiratory disease such as atelectasis, pneumonia (bacterial, viral or aspiration), or pulmonary embolism.

NMDs may result in respiratory insufficiency with 3 potential mechanisms.[2,3] A combination of these mechanisms is often implicated in an individual patient:

1. Weakness of the upper airway muscles. Weakness of the oropharyngeal muscles and tongue may result in impaired swallowing, which predisposes to aspiration of the food or respiratory secretions. Aspiration then results in atelectasis and pneumonia. Paralysis of the vocal cords and significant weakness of the tongue and pharyngeal muscles may also result in partial upper airway obstruction.[2,4]
2. Weakness of the inspiratory and expiratory muscles. The diaphragm, intercostal muscles, and accessory muscles are the main muscles of inspiration (**Fig. 2**). Weakness of these muscles may result in abnormal sigh mechanism, atelectasis caused by decreased lung expansion, and subsequent ventilation/perfusion (V/Q) mismatch. Hypoxemia may be the result of V/Q mismatch early in the course of the respiratory failure. The relative contribution of different inspiratory muscles changes in different positions. The diaphragm is the most important contributor in the supine position; therefore, diaphragmatic weakness is often associated with orthopnea. Progressive weakness of the inspiratory muscles leads to a decreased tidal volume. Compensatory tachypnea develops to maintain normal minute ventilation. This persistent tachypnea and increased work of breathing of the already weakened respiratory musculature may eventually lead to muscle exhaustion, with the evolving inability to maintain a normal minute ventilation,

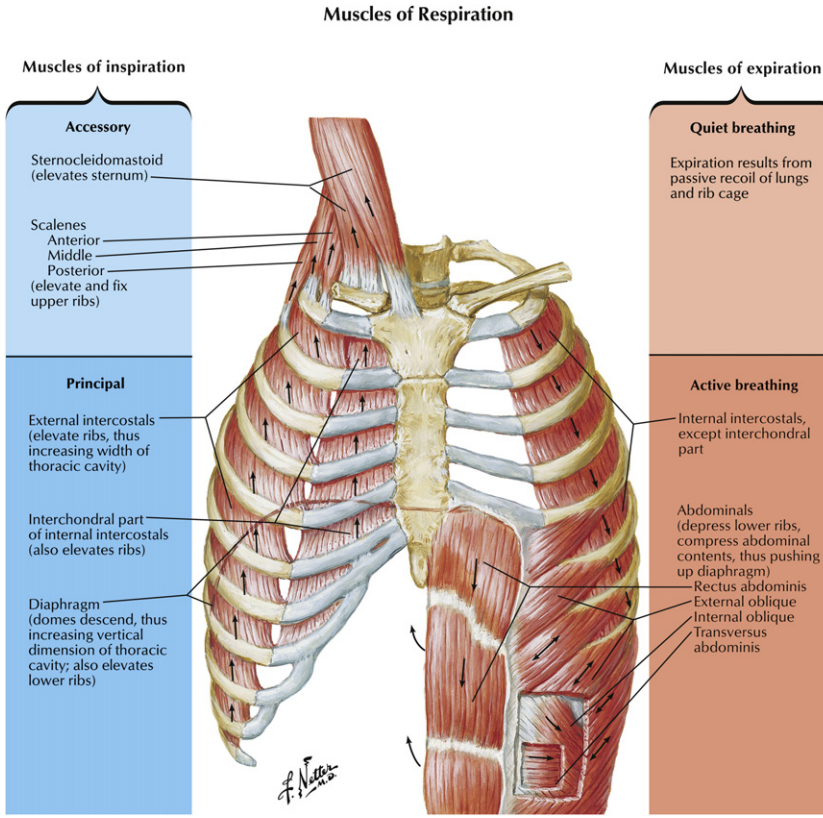

Fig. 2. Inspiratory and expiratory muscles. (*Courtesy of* Netter Images; with permission.)

resulting in progressive hypercapnia and respiratory acidosis. Hypoxemia develops in an earlier stage of the respiratory failure than CO_2 retention (hypercapnia). The latter is usually present later in the course, and is associated with significant weakness and fatigue.[5,6] Weakness of the expiratory muscles (ie, internal intercostals and abdominal muscles [see **Fig. 2**]), results in impaired coughing and clearance of respiratory secretions, which leads to mucous plugging, atelectasis, and pneumonia. Adequate strength of the inspiratory and expiratory muscles is essential for an effective cough. There should also be coordination between the muscles of the upper airways and the expiratory muscles so that the glottis opens during a forceful contraction of the expiratory muscles.

3. Concomitant cardiopulmonary disease. Patients with NMD often have a concomitant cardiomyopathy and congestive heart failure. They may also develop aspiration pneumonia and atelectasis, as mentioned earlier. The latter further decreases the lung compliance and increases the workload on the already weak muscles. Immobility may result in deep vein thrombosis and subsequent pulmonary embolization.

Sleep exacerbates the hypoventilation associated with respiratory muscle weakness. The rapid eye movement (REM) stage is associated with hypotonia and flaccidity of the accessory muscles. Therefore, patients with diaphragmatic weakness may develop hypoxia and hypercapnia during the REM stage, if they sleep in the supine position. As the respiratory muscle weakness deteriorates, hypoventilation develops during the other stages of sleep, followed by wakefulness.[7]

GENERAL APPROACH TO A PATIENT WITH IMPENDING RESPIRATORY FAILURE

When confronted with a patient with symptoms of respiratory failure, the first step is to secure the airways, provide adequate oxygenation and stabilize the hemodynamic status.[1] It should be decided whether the patient has respiratory insufficiency, and if so, whether intubation and mechanical ventilation are needed. A short history often reveals the apparent cause (ie, a cardiopulmonary disease, a neurologic disorder, or a combination of both).

The symptoms and signs that herald an impending respiratory failure include dysphagia, cough after swallowing, dysphonia, shortness of breath at rest or with minimal exertion, orthopnea, tachycardia, tachypnea, shallow breathing, use of accessory respiratory muscles, and paradoxic breathing. Weakness of the trapezius and the truncal muscles (including the neck flexors and extensors) is usually associated with significant weakness of the diaphragm and other respiratory muscles. A single breath count test may be used to assess for poor respiratory reserve.[2,3,6] Counting out loud in a single breath after a deep inspiration, an individual with a normal respiratory reserve can count to about 50. Being able to count to 25 and 10 roughly correlates with a forced vital capacity (FVC) of greater than 2L and 1L, respectively. Counts less than 15 are associated with substantial respiratory compromise.[6] Staccato speech (interrupted talking) is another clinical evidence for low and impaired respiratory reserves. Dysphagia can be tested clinically by observing the patient after swallowing 88.7 mL (3 oz) of water. Coughing implicates the dysfunction of the upper airways, leading to the aspiration of oropharyngeal content, and the necessity of withholding oral intake. Because FVC decreases about 10% in the supine position compared with sitting in nonobese individuals,[8] diaphragmatic weakness may present with orthopnea and nocturnal desaturation, because the diaphragmatic contribution diminishes during sleep.[2]

Patients should undergo immediate endotracheal intubation and mechanical ventilation if they present with respiratory or cardiac arrest, shock, impaired consciousness, respiratory distress, or evidence of active aspiration caused by the weakness of the upper airways. Patients with the weakness of the bulbar or respiratory muscles who do not have these criteria for intubation should be closely monitored, both by clinical measures and when practical and possible in the clinical setting, by spirometry and measurements of respiratory muscle strength. Intubation may then become necessary if the respiratory status continues to deteriorate.

When practical in the clinical situation, the pulmonary function tests (PFTs) to be monitored at regular intervals are the FVC, negative inspiratory force (NIF, also known as maximal inspiratory pressure [Pi max]) and positive expiratory force (PEF, or maximal expiratory pressure [Pe max]), obtained by respiratory muscle strength testing. NIF predicts the ability to maintain adequate alveolar ventilation and the PEF predicts the ability to cough and clear the airways. These tests may be performed in a pulmonary function laboratory or at the bedside with suitable equipment. NIF can be measured in the intubated patients in a critical care unit by qualified respiratory therapists. It has been suggested that PEF is the most sensitive parameter to assess for respiratory weakness in chronic NMD.[9] However, FVC and NIF are simpler to use in critically ill patients, and assess the diaphragmatic function.[6]

FVC is normally about 60 to 70 mL/kg; specific values for a given patient are dependent on age, race, and height and should be expressed as a percentage of predicted for a given patient.[10] FVC of 30 mL/kg (50%–60% of predicted) is associated with a weak cough. Subjective dyspnea also occurs when FVC is less than 30 mL/kg, but there is variability between the patients based on the age and the presence of underlying cardiopulmonary disease.[5,6] FVC less than 25 mL/kg is associated with a weak sigh (and development of atelectasis and hypoxemia) and FVC of 15 mL/kg or 1L (<30%–35% of predicted) is considered an indication for mechanical ventilation[2,6] in the appropriate clinical setting. FVC and NIF may be spuriously low if there is significant weakness of the facial and bulbar muscles or if there is significant air leak around the device mouthpiece during testing. Tidal volume changes only slightly in the early stages of respiratory failure but may decrease significantly with advanced neuromuscular weakness. Other less commonly used PFTs include peak cough flow rate (PCFR) and sniff nasal inspiratory pressure (SNIP).

DIAGNOSTIC APPROACH TO THE UNDERLYING NMD

History

A focused history should be obtained from the patient or family or by reviewing the medical records.[1] The following aspects are especially important:

1. A known underlying NMD: patients with amyotrophic lateral sclerosis (ALS) inexorably develop respiratory failure as a result of disease progression or aspiration. Patients with dystrophinopathy predictably become ventilator dependent later in the course, and myotonic dystrophy is associated with respiratory muscle weakness, as well as sleep-related breathing disorder and central hypoventilation.[11] Previous episodes of generalized weakness may suggest hypokalemic periodic paralysis or myasthenia gravis (MG) crisis, and previous episodes of rhabdomyolysis may denote an underlying metabolic myopathy affecting the glycogen or lipid pathways, such as carnitine palmitoyl transferase type II (CPT-II) deficiency.
2. A preexisting medical disease: an underlying cancer may suggest a paraneoplastic syndrome such as Lambert-Eaton myasthenic syndrome (LEMS), MG, or rarely, paraneoplastic motor neuronopathy. On the other hand, neoplastic infiltration of

the nerve roots and the peripheral nerves often occurs with lymphoid malignancies and metastatic carcinoma. History of monoclonal gammopathy may be present in patients in chronic inflammatory demyelinating polyneuropathy (CIDP) and POEMS (polyneuropathy, organomegaly, endocrinopathy, M spike, skin changes). Patients with bone marrow transplantation are predisposed to autoimmune disease like MG and Guillain-Barré syndrome (GBS). Human immunodeficiency virus (HIV) infection may be associated with GBS, CIDP, myositis, HIV myopathy, and polyradiculopathy. Polyradiculopathy may be infectious (eg, cytomegalovirus) or malignant (eg, lymphoma). Critical illness neuropathy and myopathy (CIN/M) are the most common causes of weakness in critically ill patients in the intensive care unit (ICU) (see later discussion).

3. Illicit substance use and alcoholism could be associated with rhabdomyolysis.
4. Recent respiratory or gastrointestinal infections could be present in patients with GBS or MG exacerbation. Gastrointestinal symptoms are also seen in botulism, and abdominal pain often precedes the onset of respiratory weakness in acute intermittent porphyria.
5. History of recent major surgery may suggest GBS and CIN/M.[12]
6. Medications: a large proportion of patients with cancer or history of transplantation who are admitted to the ICU have been treated with neurotoxic medications (**Box 1**). However, toxic neuropathy is generally not a common cause of respiratory failure. Furthermore, several medications are implicated in precipitation of MG

Box 1
Some of the drugs and toxins that may be associated with weakness as a result of polyneuropathy

Vinca alkaloids (vincristine, vinblastine)
Taxanes (taxol)
Platinum compounds (cisplatin, oxaliplatin)
Suramin
Tacrolimus, sirolimus
Thalidomide
Bortezomib
Amiodarone
Metronidazole
Nitrofurantoin
Tumor necrosis factor α blockers
Gold
Metals (arsenic, lead, inorganic mercury, thallium)
Hydrocarbons (n-hexane)
Buckthorn
Diphtheria
Saxitoxin
Tetrodotoxin
Tick paralysis (North American type)

crisis (**Box 2**). Barbiturates and several other antiepileptics, sulfonamides and other antibiotics, and a large number of other medications have been associated with precipitation of porphyria attack.

7. Diet: fasting and low carbohydrate intake may precipitate a porphyria attack, as well as weakness and rhabdomyolysis in patients with a variety of metabolic muscle diseases such as CPT-II. Recent intake of a high-carbohydrate diet is often encountered before an episode of paralysis in hypokalemic periodic paralysis. Intake of canned food and seafood may precede botulism and saxitoxin poisoning, respectively. Intake of the buckthorn fruit has rarely been implicated in acute neuropathy.

Examination

The accurate assessment of the muscle weakness in patients who are critically ill is often limited by the lack of cooperation. In these patients, inspection may reveal lack of spontaneous movements, muscle involuntary activity (fasciculations, myokymia), and muscle atrophy.[13] Generalized areflexia and hypotonia suggest demyelinating neuropathy (ie, GBS) or polyradiculopathy. Myalgia and muscle tenderness may represent myositis or rhabdomyolysis. **Table 1** summarizes the patterns of muscle weakness in different classes of NMD.

Electromyography and Nerve Conduction Study

Electromyography (EMG) is a valuable tool in the diagnosis of NMDs. It should preferably be conducted in the neurophysiology laboratory, where the electrical interference is minimal. On the other hand, EMG is commonly conducted in critically ill patients in the ICU. **Table 2** summarizes the EMG characteristics of different categories of NMD.

Other Workup

Other laboratory testing, including a nerve and muscle biopsy, is often needed to establish the diagnosis of an NMD. Such a laboratory workup should be tailored to

Box 2
Drugs associated with neuromuscular junction impairment or worsening of MG symptoms

- Antibiotics: aminoglycosides, colistin, polymyxin, macrolides, quinolones, imipenem, ciprofloxacin, tetracyclines
- Antiarrhythmics: procainamide, quinidine, lidocaine, trimethaphan
- Neuromuscular junction blockers (succinylcholine, vecuronium)
- Quinine
- Phenytoin
- Immunosuppressants: steroids, cyclosporine
- Antirheumatics: chloroquine, D-penicillamine
- Psychotropics: lithium, chlorpromazine
- Calcium channel blockers
- β-Blockers
- Magnesium
- Iodinated contrast

Table 1
Clinical characteristics of different categories of NMD, based on the localization of the lesion in a motor unit

Disease Category	Clinical Characteristics
Motor neuronopathy	Muscle atrophy Fasciculations Frequent involvement of bulbar muscles Lack of sensory signs and symptoms DTRs: decreased or increased ± pathologic reflexes Lack of ocular motor involvement until late in the course
Polyradiculopathy and neuropathy	Loss of deep tendon reflexes Motor and sensory impairment ± Ocular motor involvement ± Autonomic involvement
Neuromuscular junction disorder	Significant ocular motor involvement Frequent involvement of bulbar muscles Proximal → distal limb weakness Muscle atrophy usually not present DTRs: normal or decreased
Myopathy	Proximal → distal limb weakness DTRs: normal or decreased ± Myalgia ± Rhabdomyolysis

Abbreviation: DTR, deep tendon reflex.

an individual patient, based on the clinical and EMG findings. The clinical and laboratory features of different NMDs are described in **Tables 3–6**.

GBS

GBS is an acute polyradiculoneuropathy caused by autoimmunity against the structural components of the peripheral nerves.[28] Acquired inflammatory demyelinating polyneuropathy (AIDP) is the most common subtype of GBS in the United States and Europe. Axonal subtypes, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy occur in less than 10% of cases in North America and Europe.[28,29] AMAN is particularly common in China, and another variant, Miller Fisher syndrome (MFS), is more prevalent in Japan.[28,29] AIDP is characterized by progressive weakness, with maximal weakness present within 4 weeks, but usually within 2 weeks after the onset.[30,31] The weakness typically affects both proximal and distal limb muscles and frequently the truncal and respiratory muscles. Reflexes are typically absent early in the course. Facial diplegia is seen in 70% of patients.[29] Ocular motor involvement is less common, except in patients who are positive for the GQ1b antibody, including those with MFS. Sensory symptoms are commonly present, including severe pain in some patients.[29] Dysautonomia, resulting from hypoactivity or hyperactivity of the sympathetic and parasympathetic systems, occurs in about two-thirds of patients. Although mild in most patients, dysautonomia can be severe and even fatal. The symptoms may include severe fluctuations in blood pressure, heart arrhythmia, abnormal pupillary response, bladder atonia, and ileus.[29,32]

A history of a respiratory or gastrointestinal tract infection 3 weeks or less before the onset is present in about two-thirds of patients with AIDP.[29] *Campylobacter jejuni* is the most commonly encountered pathogen, and is associated with seropositivity to IgG GM1, an axonal form, and less favorable prognosis.[33–36] Cytomegalovirus is the

Table 2
EMG characteristics in different categories of NMD

Disease Category	EMG-NCS Features
Motor neuronopathy	Reduced CMAP amplitudes Normal or mildly reduced motor CV Normal SNAPs Fibrillations, positive waves, and fasciculations in multiple myotomes Reduced recruitment, neurogenic MUs
Polyradiculopathy and neuropathy	*Demyelinating:* Significant slowing of CV Marked prolongation of distal latencies Conduction block, temporal dispersion SNAPs abnormal Fibrillations and positive waves if there is concomitant axonal loss *Axonal:* Reduced CMAP amplitudes Normal or mildly reduced motor CV SNAPs abnormal (except for AMAN) Fibrillations and positive waves in multiple myotomes Reduced recruitment, neurogenic MUs
Neuromuscular junction disorder	*Postsynaptic:* Normal baseline CMAP amplitude Normal SNAPs Decrement of CMAP amplitude with low frequency (2–5 Hz) repetitive stimulation Needle EMG normal, or may show neurogenic or myopathic units *Presynaptic:* Low baseline CMAP amplitude Facilitation of CMAP amplitude after brief (ie, 10 s) exertion Facilitation of the CMAP amplitude with high-frequency (20–50 Hz) repetitive stimulation Decrement of the CMAP amplitude with low-frequency (2–5 Hz) repetitive stimulation
Myopathy	CMAP amplitude reduced or normal SNAPs normal ± Fibrillations and positive waves Myopathic (short duration ± polyphasic) units Early recruitment

Abbreviations: CMAP, compound muscle action potential; CV, conduction velocity; MU, motor unit; SNAP, sensory nerve action potential.

second most common infection associated with GBS.[33,36] Other more commonly encountered pathogens are Epstein-Barr virus, *Mycoplasma pneumoniae*, HIV, and *Haemophilus influenzae*.[29]

Respiratory failure is one of the most serious short-term complications of GBS, and occurs in about 30% of patients.[37] A large proportion of patients with GBS develop phrenic neuropathy, although the accessory nerve is spared except in the more severe cases.[6] About 25% of patients with GBS who are unable to walk need mechanical ventilation[29]; and intubation and mechanical ventilation are required in 30% to 50% of patients admitted to the ICU.[37–40]

It is recommended to assess FVC every 2 to 4 hours during the day and every 4 to 6 hours at night in a patient with declining respiratory function.[6] NIF should be measured

Table 3
Clinical and laboratory features and suggested treatments of neuropathies that may cause respiratory failure

Type of Neuropathy	Clinical Features	EMG and Laboratory Findings	Treatment in the Acute Stage (Besides Supportive Care)
CIDP	Proximal and distal weakness Proximal and distal sensory impairment Progressive course >2 mo Hypertrophic polyradiculopathy (uncommon) Cranial neuropathy (uncommon)	EMG: demyelinating features High CSF protein (always >45 mg/dL) Albuminocytologic dissociation	Steroids IVIG Consider steroid sparing agents and tapering steroids
POEMS[14,15]	Polyneuropathy Organomegaly (hepatomegaly, splenomegaly, lymphadenopathy) Endocrinopathy (diabetes, hypothyroidism, gynecomastia) Skin lesions (edema, clubbing, hypertrichosis, hyperpigmentation)	EMG: severe, primarily demyelinating neuropathy, but axonal loss always present M spike (usually IgG or IgA paraprotein, λ chain in >95%). $\pm$ Sclerotic plasmacytoma $\uparrow$ serum VEGF Multiorgan failure, ascites, pleural effusion,	Irradiation or resection of plasmacytoma Melphalan, dexamethasone, IVIG Consider autologous stem cell transplantation, thalidomide or bevacizumab
Vasculitis and collagen vascular disease	Underlying systemic vasculitis (eg, polyarteritis nodosa) may be present Multifocal neuropathy which becomes confluent Sensory and motor involvement Neuropathic pain	EMG: axonal polyneuropathy or mononeuropathy multiplex Positive serology (ANCA, ANA, SSA, SSB, others) Nerve and muscle biopsy	Steroids Immunosuppressants
Saxitoxin, tetrodotoxin[16–18]	Onset within hours after intake of contaminated mussels, oysters, or clam (saxitoxin), and fish (tetrodotoxin) Limb, bulbar, and respiratory weakness Headaches, encephalopathy, ataxia, nausea, vomiting Cardiac arrhythmias Mechanism: blockage of Na channels	EMG: conduction block and small amplitude CMAP and SNAP Toxin detection in urine	Induced emesis to remove unabsorbed toxin

Tick paralysis North American types[19]	*Dermacentor variabilis* (dog tick), *Dermacentor andersoni* (wood tick) Children predominantly affected Ascending paralysis, areflexia, ataxia, truncal, bulbar weakness, and respiratory failure Progression over hours to few days	EMG: prolonged latency, slow CV (axonal range), low CMAP and SNAP amplitudes CSF protein normal Potential mechanism: impaired saltatory conduction at the terminal axons	ICU admission and close observation Tick removal results in rapid and complete recovery
Hypophosphatemia	Risk factors: hyperalimentation without adding inorganic phosphate,[20,21] anorexia/bulimia,[22] treatment of diabetic ketoacidosis,[23] hemodialysis[24] Generalized weakness, respiratory muscle weakness, rhabdomyolysis, polyneuropathy, encephalopathy	EMG: ± polyneuropathy with either axonal or demyelinating features[20,21]	Rapid improvement with parenteral phosphate supplementation, suggests a reversible metabolic impairment of the myofiber function in most cases
Acute intermittent and variegate porphyria[25]	Abdominal pain, followed by progressive weakness Motor → sensory, ± respiratory failure, bulbar and facial muscle weakness CNS demyelination Psychiatric features Dysautonomia Recent use of specific medications and hormones	EMG: axonal, predominantly motor neuropathy ↑ Urinary porphobilinogen and σ aminolevulinic acid Porphobilinogen deaminase assay	Intravenous glucose and heme arginate Symptomatic treatment of pain (eg, meperidine), Gastrointestinal symptoms
Diphtheria[26,27]	Polyneuropathy occurs in at least 15%, 20% of which develop respiratory failure Onset of neuropathy weeks after the onset of infection Bulbar weakness universal ± Ocular motor weakness Sensory and autonomic impairment in all of the patients Cardiomyopathy (often fatal)	EMG: prolonged distal motor latencies, ± slow motor conduction velocities CSF: high protein, mildly increased cell count ± albuminocytological dissociation Positive throat culture for *Corynebacterium diphtheriae*	Diphtheria antitoxin within the first 2 d of onset

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; CV, conduction velocity; VEGF, vascular endothelial growth factor; SSA and SSB, Sjogren syndrome associated antibodies.

Table 4
Clinical and laboratory features and suggested treatments of neuromuscular junction disorders that may cause respiratory failure

Neuromuscular Junction Disorder	Clinical Features	Treatments (Other than Close Monitoring and Respiratory Care)
LEMS[75,76]	Muscle weakness (especially proximal lower extremity weakness) Ptosis (ophthalmoparesis uncommon) Hyporeflexia Dysautonomia Muscle pain Association with small cell lung cancer in two-thirds of patients Antibodies to P/Q voltage gated calcium channels in 90% of patients	Treatment of small cell lung cancer 3,4-DAP PE or IVIG Avoid calcium channel blockers
Botulism[77–79]	Abdominal pain, nausea, or vomiting, diarrhea preceding weakness Bulbar and ocular motor involvement Respiratory failure in 20%–30% of patients Autonomic impairment (unreactive pupils, urinary retention, fluctuations in pulse and blood pressure) Recent intake of canned food, soft tissue trauma, and infected wounds	Close monitoring in ICU Administration of botulinum antitoxin
Hypermagnesemia[80,81]	Underlying renal failure, laxative abuse, magnesium-containing antiacids, tocolysis Respiratory depression Quadriparesis	Rapid improvement with calcium gluconate intravenously
Organophosphate poisoning[82,83]	Suicidal attempt or accidental exposure. Respiratory failure common, bulbar weakness, quadriparesis, fasciculations, cramps, miosis	Intravenous atropine and pralidoxime
Snake venom[84–86]	Progressive bulbar paralysis and respiratory failure, ptosis, and ophthalmoparesis Pathogenesis: *Bungarus* sp: presynaptic (β-BTX), postsynaptic: nicotinic AChR (α-BTX and γ-BTX); Cobra: nicotinic AChR (α-cobra toxin)	Appropriate snake antitoxin Supportive care of respiratory failure and rhabdomyolysis (if present)

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Table 4
(*continued*)

Neuromuscular Junction Disorder	Clinical Features	Treatments (Other than Close Monitoring and Respiratory Care)
Tick paralysis Australian type[87]	*Ixodes holocyclus* (marsupial tick) Rapidly progressive ascending paralysis, with early cranial nerve involvement Respiratory failure common and potentially fatal EMG: low motor amplitudes, normal sensory responses; normal repetitive stimulation Possible mechanism: interference by neurotoxin with ACh release an NMJ (similar to botulinum toxin)	Antitoxin to be injected before tick removal More severe, and longer time to recovery than the North American type ICU admission and respiratory support in the acute stage
Prolonged neuromuscular block[88]	Underlying kidney or liver failure, hypermagnesemia, medication interaction (eg, sevoflurane), cholinesterase or pseudocholinesterase deficiency Use of a neuromuscular blocker (eg, mivacurium, rapacuronium) Generalized weakness, ophthalmoparesis, ptosis, failure to wean	Avoidance of use of neuromuscular blocker

Abbreviations: ACh, acetylcholine; BTX, bungarotoxin; DAP, diaminopyridine; NMJ, neuromuscular junction.

at the same time if possible, because it may be more sensitive to declines in respiratory function.

The patients with significant respiratory muscle weakness may deteriorate clinically, as shown by distress, fatigue, accessory muscle use, and thoracoabdominal dyssynchrony, before such deterioration is reflected in either arterial blood gas (ABG) or pulmonary function measurements. Therefore, intubation, either elective or emergent, is a bedside clinical judgment.

Because emergency intubation substantially increases the risk of complications such as aspiration and hypoxemia, it is essential to anticipate the need for intubation and mechanical ventilation and proceed with elective intubation in selected patients. Criteria proposed for elective intubation and MV in patients with GBS include significant respiratory distress, fatigue, sweating, tachycardia, active aspiration, and FVC of 10 to 12 mL/kg (<30%–35% of predicted), and $Paco_2$ greater than 50 mm Hg. Elective intubation should be considered in the presence of a higher FVC if the condition is rapidly deteriorating, if there is inefficient cough, inability to clear bronchial secretions despite vigorous chest physiotherapy,[38,39,41] or if the patient has a significant concomitant morbidity such as active cardiac ischemia or heart failure.

Predictive parameters for mechanical ventilation in GBS include rapidly progressive course as manifested by time to peak disability less than 7 days, time from the onset of symptoms to hospitalization less than 7 days, and more than 30% reduction of vital capacity, NIF, and PEF.[40,42] Significant bulbar dysfunction, facial weakness, impaired cough, dysautonomia, and inability to lift the elbow or head off the bed are other suggested predictors of need for mechanical ventilation. On the other hand, an FVC less

Table 5
Clinical and laboratory features and suggested treatments of diseases of the motor neuron that may cause respiratory failure

Disease of the Motor Neuron	Clinical Features and Pertinent Paraclinical Findings	Treatment in the Acute Phase
Poliomyelitis	Myalgia and meningoencephalitis, followed by asymmetrical paralysis ± bulbar and respiratory muscle weakness ± dysautonomia EMG: ↓ CMAP amplitudes, denervation in multiple myotomes, CSF: ↑ WBC (neutrophils early on), ↑ protein, normal glucose Serology: ↑ IgM titer in CSF	Supportive treatment
West Nile meningoencephalitis[89]	Motor neuronopathy (similar to poliomyelitis) Asymmetrical weakness, ± diaphragm weakness, facial weakness common Meningoencephalitis (headaches, ataxia, seizures) EMG: CSF: similar to polio + ↑ IgM titer in serum and CSF	Supportive treatment Mortality higher in age >75 y
Tetanus[90]	Risk factors: lack of adequate vaccination, puncture wounds, tongue piercing, poor hygiene childbirth (for the neonatal form) Severe, painful muscle spasms that may last seconds to minutes Generalized form: opisthotonus, generalized spasms, respiratory failure, dysautonomia, ± rhabdomyolysis and renal failure Milder, local forms: trismus, face muscle spasms (risus sardonicus), dysphagia, neck stiffness, and local limb spasms EMG: continuous high-frequency motor unit discharges during periods of spasms Wound culture positive in 30%–50% Mechanism: tetanospasmin induces sustained firing of motor neurons as a result of impaired release of inhibitory neurotransmitters (GABA and glycine)	Human tetanus immunoglobulin administration Treatment of respiratory failure, rhabdomyolysis, cardiac arrhythmias and dysautonomia Antispasmodics: diazepam, baclofen, magnesium sulfate Antibiotic and surgical treatment of wound

Abbreviations: CMAP, compound muscle action potential; CSF, cerebrospinal fluid; GABA, γ-aminobutyric acid; WBC, white blood cells.

than 20 mL/kg, NIF less than negative 30 cm H_2O and PEF less than 40 cm H_2O (20/30/40 rule) during the course of hospitalization are other PFT parameters that have been suggested to predict intubation and mechanical ventilation.[42,43]

Noninvasive, positive pressure ventilation (NIV or NIPPV) is not a good choice in patients with respiratory failure and significant bulbar muscle weakness, because there is increased risk of aspiration or collapse of the upper airways.[2] NIV should also be avoided in patients who are likely to need a long duration of respiratory support. Other important supportive management issues include deep vein thrombosis and peptic ulcer disease prophylaxis, and appropriate treatment of the cardiac arrhythmias, fluctuations in the blood pressure, ileus, and urinary retention.

Plasma exchange (PE) and intravenous immunoglobulins (IVIG) are both proved to be effective in the treatment of GBS.[28,44] PE is more effective when it is given early in the course, and the usual regimen is a total exchange of about 5 plasma volumes of 50 mL/kg during 1 to 2 weeks.[28,45] IVIG has replaced PE as the preferred method of treatment in many hospitals, after a large randomized clinical trial showed its equal efficacy to PE.[46] The usual dose is 2 g/kg over a 3 to 5-day period.[45] The mortality of GBS is estimated at 3% to 10%; the most common causes of death are the complications of dysautonomia and respiratory failure.[29,32] **Table 3** summarizes the clinical and paraclinical features of some of the other neuropathies that could be associated with respiratory failure.

GENERALIZED MG

Generalized MG is a commonly encountered neuromuscular cause of respiratory failure. Involvement of the facial and oropharyngeal muscles happens during the course of the disease in most patients, causing facial weakness, dysphagia, and dysarthria (nasal speech). MG crisis is referred to exacerbation of the generalized weakness, with associated respiratory insufficiency and the need for mechanical ventilation. MG rarely presents with isolated stridor or respiratory failure.[47–49] The course of MG is unpredictable, especially in the first 2 years of diagnosis. MG crisis occurs in approximately 15% to 20% of patients some time during the course, but most often during the first year after the onset of symptoms.[50] MG crisis may be precipitated by the disease progression, treatment with high-dose steroids, anticholinesterases, and other medications that affect the neuromuscular transmission (see **Table 3**).[3,50,51] Intercurrent infections, pregnancy, surgery, and other sorts of stress (including emotional) are other causes of MG crisis.

MG diagnosis is usually made based on the clinical grounds and seropositivity to the acetylcholine receptors (AChR) autoantibodies, present in about 85% of the generalized cases.[52] Antibodies to the muscle specific kinase are found in about 40% of the seronegative patients.[53] EMG is useful to differentiate MG from neuropathies such as GBS, myopathies, motor neuron diseases (MNDs), and other neuromuscular transmission diseases such as LEMS and prolonged effect of the neuromuscular blockers (see **Table 1**). The edrophonium (Tensilon) test can be used at the bedside to diagnose MG.[52,54] Edrophonium is given intravenously, and the patient is watched for immediate improvement of the MG symptoms, usually ptosis or ocular movements. If the appropriate target symptoms are present, the sensitivity is 71% to 95%.[54] Cardiac monitoring is strongly recommended, because there is a low risk of serious side effects like bradycardia and asystole. It has been suggested that because of its maximum effect at 15 to 30 minutes, 2 mg of intramuscular neostigmine could provide better diagnostic results in patients with respiratory weakness, because the PFT data can be repeated during that interval.[6]

Table 6
Clinical and laboratory features and suggested treatments of some of the muscle diseases that could cause acute respiratory failure

Type of Myopathy	Clinical Features	EMG and Laboratory Findings	Treatment in the Acute Stage (Besides Supportive Care)
Polymyositis, dermatomyositis[91–93]	Proximal → distal limb weakness usually present Respiratory failure caused by diaphragm and intercostal weakness can rarely be the predominant symptom Skin rash in dermatomyositis Cardiomyopathy, interstitial lung disease	EMG: myopathies, with spontaneous activity ↑ CPK Muscle biopsy Underlying malignancy should be excluded in polymyositis >50	Steroids IVIG
Rhabdomyolysis[84,94,95]	Proximal → distal weakness, and myalgia ± respiratory failure Causes: Drugs: statins, colchicine, clofibrate, others Cocaine, heroin, alcohol Neuroleptic malignant syndrome, serotonin syndrome Snake venom (*Bungarus candidus* and *multicinctus*), cobra, coral, rattlesnake Wild mushroom Tetanus	Markedly ↑ CPK Myoglobinuria, kidney dysfunction	Monitor renal function, IV hydration, alkalinize urine Specific antivenom immunoglobulin in the case of envenomation
Acid maltase deficiency[96,97]	Diaphragmatic weakness and respiratory failure common in the adult form ± proximal → distal weakness, paraspinal atrophy, winging scapula Sleep-disordered breathing common	EMG: myopathic units, fibrillations, myotonic discharges, especially in the paraspinal muscles CPK: normal to markedly ↑, urine hexose tetrasaccharide ↑ Muscle biopsy or assessment of α glucosidase activity in blood or skin fibroblasts	BIPAP Long-term IV enzyme replacement

Mitochondrial myopathy[98–100]	Respiratory failure could be central (↓ respiratory drive) or as a result of respiratory muscle weakness Symmetric ophthalmoparesis and ptosis Proximal → distal weakness ± Cardiomyopathy, diabetes, seizures, neuropathy	EMG: ± myopathic units CPK: normal or mild ↑ ± ↑ lactate Diagnosis by muscle biopsy	Supportive care (mechanical ventilation vs BIPAP)
Deficiency of β oxidation or fatty acid transport enzymes[101–104]	Respiratory failure rare in very long chain acyl-CoA, CPT-II Recurrent rhabdomyolysis ± muscle weakness Precipitating factors: fasting, infections, endurance exercise	↑ urinary dicarboxylic acids Assessment of blood acylcarnitines Enzyme activity in the muscle	Monitor renal function, IV hydration, alkalinize urine
Hypokalemic periodic paralysis[105,106]	Proximal → distal weakness, ↓ reflexes Cranial nerves not affected Respiratory failure rare Precipitated by high-carbohydrate diet, rest after exercise, and medications such as insulin and β agonists	↓ K during attack Thyrotoxicosis often present CPK: normal or mildly ↑ EMG: CMAP amplitude diminished during attack and insertional activity decreased during attack, ± fibrillations and myopathic units	KCl supplementation during attack Prophylaxis: acetazolamide and dichlorphenamide Secondary causes of hypokalemia to be excluded

Abbreviations: CMAP, compound muscle action potential; CPK, creatine phosphokinase; IV, intravenous.

Respiratory failure in MG may present with tachycardia, anxiety, restlessness, and tachypnea in the early stage. Later in the course and with worsening hypoxemia and the emergence of hypercapnia, patients develop cyanosis, encephalopathy, and headaches. MG patients with questionable status should be closely monitored in the ICU with repeated clinical evaluation as well as bedside FVC and NIF.[5] However, given the fluctuating nature of the weakness, it is often difficult to predict the need for mechanical ventilation in MG, even with close monitoring.[2,55] An ABG measurement should be obtained if there is suspicion of evolving respiratory failure. Intubation is recommended with marginal and declining respiratory status, FVC less than 15 mL/kg, Pa_{O_2} less than 60 mm Hg and Pa_{CO_2} greater than 50 mm Hg.[6] Oral intake should be stopped, and intubation should also be considered in patients with aspiration or significant weakness of the oropharyngeal muscles. In a retrospective study, the mortality of MG crisis was 4% and the parameters that predicted prolonged intubation included a preintubation bicarbonate level greater than 30 mg/dL,peak vital capacity less than 25 mL/kg on day 1 to 6 after intubation, and age older than 50 years.[50]

The use of NIV (intermittent bilevel positive airway pressure [BIPAP]) early in the course of the MG crisis may prevent the development of atelectasis and lead to a lesser need for intubation and mechanical ventilation. In 2 retrospective studies on respiratory failure in MG, BIPAP prevented intubation and mechanical ventilation in 60% to 70% of the trials.[56,57] Hypercapnia (a P_{CO_2} >45 mm Hg) was a strong predictor of the failure of BIPAP in one of those studies.[57]

PE and IVIG with the same dose mentioned under GBS have been shown to be effective in myasthenic crisis.[58] Although PE was more effective for improving the respiratory status than IVIG in a study, it was also associated with more side effects and increased length of ICU stay.[59] Starting a high dose of corticosteroids is a potential cause of MG crisis, and should be avoided unless the patient is already on mechanical ventilation. If the patient is on a low dose of prednisone, the dose should be increased, preferably after the respiratory function has started to improve with either PE or IVIG. Anticholinesterase inhibitors such as pyridostigmine should be withheld in patients on mechanical ventilation for the potential cardiovascular side effects such as arrhythmias, increasing bronchial secretions, and increased airway resistance.[58] Pyridostigmine, which is also available in the intravenous form, may be restarted when the patient is being weaned off. It can be started at 30 mg orally every 3 to 4 hours, and increased to 60 mg every 3 to 4 hours. Higher doses (up to 120 mg every 3–4 hours) are sometimes used; however, higher doses often do not improve the symptoms, and the weakness may paradoxically deteriorate.[58] **Table 4** summarizes the clinical and laboratory characteristics of other more commonly encountered neuromuscular junction transmission diseases.

ALS

MND is characterized by progressive degeneration of the motor neurons. The less common variants of MND (spinal muscular atrophy and spinobulbar muscular atrophy) are diseases of the lower motor neurons (which are located in the motor brainstem nuclei and the anterior horns of the spinal cord). On the other hand, ALS is characterized by the progressive degeneration of the lower and upper motor neurons. Respiratory failure emerges in almost all patients with ALS, and is the cause of death in most of these patients.[60,61] Respiratory muscle weakness is predominantly secondary to diffuse denervation (lower MND); however, upper motor neuron impairment is also implicated in the respiratory symptoms in ALS.[62,63] Bulbar muscle dysfunction caused by lower motor neuron (bulbar palsy) or upper motor neuron (pseudobulbar palsy)

disease, also invariably complicates the clinical course of ALS.[64] Bulbar-onset ALS is more common in older patients; 43% of patients with ALS older than 70 years presented with bulbar symptoms in a study.[65] Bulbar weakness results in aspiration and impaired cough, as well as malnutrition, which leads to further weakness and atrophy of the respiratory muscles.[64] Early symptoms of respiratory failure in ALS include exertional dyspnea, orthopnea, frequent nocturnal arousals, daytime somnolence, morning headaches, and impaired memory and concentration.[63]

Because respiratory failure may even occur early in the course of ALS, the treatment plan and the patient's wish for intubation and mechanical ventilation should be discussed before an emergency situation arises.[7] Patients with ALS should be closely monitored with PFTs such as supine and upright FVC, PEF, NIF, and PCFR.[7] The efficacy of the airway mucous clearance is largely determined by the strength of the cough as assessed by the PCFR.[64,66] These tests may be spuriously low when bulbar and facial weakness is present, and when there is inadequate control of the voluntary respiratory muscles because of upper motor neuron involvement. SNIP is another method that can be effectively used in patients with significant bulbar weakness, because it does not require a tight seal around a mouthpiece.[63] SNIP has been shown to correlate with the transdiaphragmatic pressure, and SNIP less than 40 cm H_2O correlates with nocturnal hypoxemia.[67] Nighttime pulse oximetry may also provide evidence for intermittent nocturnal hypoventilation, because the hypoventilation generally deteriorates during sleep.

The timely institution of adequate nutrition through percutaneous endoscopic gastrostomy has been shown to improve the survival and the quality of life in patients with ALS.[61] The procedure-related morbidity is substantially lower when percutaneous endoscopic gastrostomy is performed with FVC greater than 50% predicted and SNIP greater than 40 cm H_2O; and the rate of procedure-associated complications (including intubation and mechanical ventilation) substantially increases in patients with more advanced respiratory failure.[61,67] The use of NIV has been recommended with the presence of signs and symptoms of respiratory failure, greater than 1 minute of nocturnal O_2 desaturation of less than 90%, FVC less than 50%, SNIP less than 40 cm H_2O, and PCFR less than 270 L/min.[63,68] Aspiration and increased secretions as a result of bulbar weakness may result in difficulties in the use of NIV in patients with ALS. Because mucous plugging could result in serious complications such as atelectasis and pneumonia, frequent chest physiotherapy, frequent suctioning, and use of assistive cough devices are recommended in patients with a weak cough.[63]

Because continuous positive airway pressure causes increased workload on the already weak respiratory muscles, it is better avoided in patients with ALS.[7] Caution should also be exercised in the use of medications that suppress the respiratory drive (such as benzodiazepines and narcotics). The use of nocturnal supplemental oxygen in patients with significant respiratory muscle weakness (including ALS) has also been shown to suppress the respiratory drive and cause hypercapnia.[63,69]

RESPIRATORY WEAKNESS IN THE ICU

In patients with respiratory muscle weakness in the ICU, it should first be determined whether the weakness preceded (and led to) the ICU admission. GBS and MG crisis are the most commonly encountered acute NMDs that result in ICU admission. On the other hand, Critical Illness Myopathy and Polyneuropathy (CIM and P) account for most patients who develop weakness (or cannot be weaned from the ventilator) after being admitted to the ICU for another reason.

In a retrospective study on 92 ICU patients who underwent EMG, 28% had a primary NMD (GBS, MG, and MND) that resulted in the ICU admission. CIM and P accounted

for 42% and 13% of the cases, respectively.[70] Electrophysiologic evidence for CIM and P was present in 50% of ICU patients with a stay of more than 3 days in another study.[71] Of patients with ICU stay of more than 1 week, 50% to 70% develop clinical CIM and P; this figure may reach 100% in patients with a long ICU stay with sepsis and end-organ damage.[71] CIM and P often emerges in the setting of treatment with high-dose corticosteroids and neuromuscular blockers. Other risk factors include sepsis, long ICU stay, encephalopathy, and need for vasopressor support.[71,72] The clinical picture consists of generalized weakness, lack of tolerance of weaning from the ventilator when the patient is off sedation, and lack of cardiopulmonary explanation. Examination reveals flaccidity and hyporeflexia, and muscle atrophy can be prominent in chronic cases. Muscle atrophy results in the prominence of the hand tendons and the tibia in patients with severe critical illness polyneuropathy (CIP).[13] Facial weakness and ophthalmoparesis are rare and these features point to other differential diagnoses (ie, MG, prolonged neuromuscular blockade, GBS).[71] Examination of the sensation is usually complicated by encephalopathy and sedation, but there is a stocking-gloves decrease of sensation when CIP is present.[13] Creatine phosphokinase (CPK) level was markedly increased in a retrospective study in about 50% during the first 5 days after the onset of the weakness, with subsequent gradual normalization.[73] The nerve conduction study may be normal, or shows abnormally low compound muscle action potential amplitudes in CIM. It reveals an axonal sensorimotor neuropathy in CIP. Abnormal spontaneous activity is seen in some cases of myopathy, and is uniformly present in the more distal muscles in CIP.[71] Direct muscle stimulation has been used to distinguish CIP and CIM (muscle is inexcitable in CIM).[74] If a muscle biopsy is performed, it may show myosin loss, myofiber atrophy, or a necrotizing myopathy (myofiber necrosis, vacuolization, and phagocytosis).[71] Minimizing the use of high doses of steroids and neuromuscular blocking agents and aggressive insulin treatment (keeping the blood sugar at 80 to 110 mg/dL) have been suggested to reduce the incidence of CIM and CIP.

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