INTRODUCTION

Neuromuscular disorders, especially acquired ICU neuromyopathy, are important contributors of morbidity and mortality in the intensive care unit (ICU). As more patients survive their acute illness due to advances in critical care medicine, acquired ICU neuromyopathy has emerged as the most common cause of muscle weakness in the modern ICU. In approximately a third of cases, an acute presentation or an acute exacerbation of the underlying chronic neuromuscular disease occurs. Guillain–Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and myopathy (acquired before ICU admission) account for the majority of chronic underlying neuromuscular disorders that are most commonly observed in the ICU.
Although neuromuscular diseases are varied in etiology and pathogenesis, all can potentially lead to life-threatening respiratory failure, primarily by affecting the pump function of respiratory muscles and impairing the ability to generate an effective cough. Thus, neuromuscular dysfunction typically presents in the ICU setting as acute respiratory failure, acute-on-chronic respiratory failure, or failure to wean from mechanical ventilation after the resolution of the acute illness. In patients with known neuromuscular disorder, acute respiratory failure is either precipitated by disease progression or an exacerbation of the underlying neuromuscular disease, or by an infection such as a community-acquired pneumonia. In patients who fail to wean from mechanical ventilation, the incidence of neuromuscular dysfunction has been reported to range from 10 to 25% in US ventilator rehabilitation units (VRU).

The severity of respiratory muscle dysfunction caused by neuromuscular diseases depends on the pattern and extent of respiratory muscle involvement (inspiratory or expiratory muscle involvement) and availability of effective medical therapy (plasmapheresis in Guillain–Barré syndrome; anticholinergic agents in myasthenia gravis). The respiratory pump may be impaired at the level of the central nervous system, spinal cord, peripheral nerve, neuromuscular junction, or respiratory musculature. Neuromuscular disorders seen in the ICU and their corresponding site of injury are listed in Table 29-1.

A thorough understanding of the neuroanatomical and pathological changes caused by the various neuromuscular disorders is fundamental in learning the essential steps toward appropriate diagnosis and treatment. In this chapter, the etiology, pathophysiology, and treatment of selected neuromuscular diseases most commonly observed in the ICU are reviewed in detail.

**TABLE 29-1**

| LEVEL OF THE MOTOR UNIT | DISORDER |
|-------------------------|----------|
| Motor neuron            | Amyotrophic lateral sclerosis |
|                         | Poliomyelitis |
| Peripheral nerve        | Guillain–Barré syndrome |
|                         | Critical illness polyneuropathy |
|                         | Shellfish poisoning |
|                         | Porphyric neuropathy |
| Neuromuscular junction  | Myasthenia gravis |
|                         | Botulism |
|                         | Hypermagnesemia |
|                         | Lambert–Eaton syndrome |
| Muscle                  | Acquired disorders |
|                         | Myoglobinuric myopathy |
|                         | Hypokalemic paralysis |
|                         | Toxic myopathy |
|                         | Acute myopathy of intensive care |
|                         | Congenital disorders |
|                         | Acid maltase deficiency |
|                         | Mitochondrial myopathy |

**CASE STUDY: PART 1**

N.C., a 38-year-old self-employed businessman, sought neurology consultation for progressive limb numbness and weakness over the past week. His symptoms started 10 days before consultation when he experienced numbness and a tingling sensation in both feet. Because he had never been sick and had always lived a healthy lifestyle, he ignored the symptoms and attributed them to the tight new moccasins his wife had given him on their tenth wedding anniversary. However, 2 days later, he began to have difficulty climbing stairs and doing his usual 10 km run. Three days before consultation, he experienced the same symptoms and weakness in both hands. He denied any swallowing difficulty. His past medical history was unremarkable except for a bout of diarrhea 2 months ago following a business trip to China.
PATHOPHYSIOLOGY OF NEUROMUSCULAR DISEASES THAT AFFECT THE RESPIRATORY FUNCTION

Various neuromuscular diseases can impair the different functional components of the respiratory system. Some diseases may affect the cortical center of breathing, whereas others predominantly affect the pump function of the respiratory muscles and chest wall to drive air in and out of the lungs. In addition, upper airway muscle weakness can lead to swallowing difficulty and recurrent aspiration that results in hypoxemia and aspiration pneumonia. The end result of the pathophysiological impairments caused by neuromuscular weakness on the respiratory system is respiratory failure (Fig. 29-1). The most typical changes in the respiratory system observed in patients with moderately advanced chronic neuromuscular dysfunction are listed in Table 29-2.

Control of Breathing

Chronic respiratory insufficiency in patients with chronic neuromuscular disorder is primarily due to respiratory muscle weakness. However, several studies have shown that some patients afflicted with congenital myopathies exhibit hypoventilation out of proportion to the severity of their respiratory muscle weakness, suggesting the possibility of impaired central respiratory drive.1

Several studies have shown that the hypoxic and hypercapnic ventilatory responses are blunted in patients with congenital myopathies.2,3 In normal individuals, the relationship between oxyhemoglobin desaturation and ventilation is linear; that is, a fall of oxygen saturation by 1% is approximately associated with a 1-L/min increase in minute ventilation. A much steeper linear increase in minute ventilation is seen during hypercarbic challenge. Thus, for every 1 mmHg rise in pCO2, ventilation increases by 2.5–3 L/min. This normal predictable increase in minute ventilation in response to hypoxia and hypercapnia may be altered in certain neuromuscular disorders. In addition to a decrease in central neural drive, a blunted ventilatory response to hypoxia and/or hypercapnia may be related to other factors such as respiratory muscle dysfunction and/or abnormal chest wall and lung mechanics.

Respiratory muscle weakness is the most common cause of chronic respiratory failure.

FIGURE 29-1

Schematic diagram of pathologic changes induced by neuromuscular disease on the respiratory system. The severity of these pathologic changes depends on the type and clinical stage of the neuromuscular disorder. FRC, functional residence capacity.
A better test of the central respiratory drive, one that is independent of respiratory mechanics, is the mouth occlusion pressure, or Pm100. Pm100 refers to the maximum negative mouth pressure generated during the first 100 ms of inspiration with complete airway occlusion. Because the Pm100 is obtained during early inspiration with only a fraction of total inspiratory time, it is not influenced by a conscious alteration in respiration. Similarly, because the Pm100 is only a fraction of the maximum inspiratory muscle strength, the result may remain valid even in the presence of moderately severe respiratory muscle weakness.

In studies using Pm100, central respiratory drive has been found to be normal or increased in patients with neuromuscular disease, despite substantial muscle weakness. Indeed, several studies have shown that despite significant reductions in respiratory muscle strength, the Pm100 in patients with Duchenne’s muscular dystrophy, myotonic dystrophy, and a variety of neuromuscular diseases is one to twofold higher than in normal controls. Similar increases in Pm100 were observed in normal volunteers after severe muscle weakness induced by the administration of curare. Thus, it appears that central respiratory drive as measured by Pm100 is preserved in most patients with neuromuscular disease.

### Respiratory Muscle Function

The respiratory muscles consist of the upper airway muscles, diaphragm, chest wall muscles, and abdominal muscles. The respiratory muscles can be further divided functionally into inspiratory and expiratory muscles. The inspiratory muscles produce rib cage expansion and generate negative intrathoracic pressure, allowing inspiratory airflow. During rest, exhalation is passive and driven by lung and chest wall recoil pressures. However, the expiratory muscles may become active during periods of increased expiratory effort, such as coughing, exercise, and airflow obstruction. The innervation of the different respiratory muscle groups and their functions are shown in Table 29-3.

Patients with moderate-to-severe respiratory muscle weakness due to neuromuscular disease often complain of fatigue, poor sleep quality, and dyspnea, especially on exertion. Ineffective cough may lead to recurrent respiratory infections. Sleep disorders, acute or chronic respiratory failure, and secondary pulmonary hypertension may result as respiratory conditions.
muscle weakness progresses and hypoxemia and hypercapnia ensue. However, a significant percentage of these patients may be asymptomatic despite the presence of significant respiratory muscle weakness. These patients can present in the ICU with acute hypercapnic respiratory failure, which is often associated with community-acquired pneumonia. Since these patients do not have prior respiratory complaints, respiratory muscle weakness is often not suspected until difficulty weaning from the ventilator is encountered. In one study, 27% of patients with moderately advanced neuromuscular disease who had severe reductions in both inspiratory and expiratory muscle function had no prior respiratory complaints. In another report, 50% of patients with severe respiratory muscle weakness due to chronic neuromuscular disease were asymptomatic. It is unclear why respiratory muscle weakness correlates so poorly with patient reported symptoms. It is possible that the presence of significant respiratory muscle weakness is masked by concomitant generalized muscle weakness and a sedentary lifestyle.

The severity and the pattern of involvement of the respiratory muscles by the different neuromuscular disorders are not uniform. Some diseases cause global respiratory muscle dysfunction, whereas others cause preferential weakness of the inspiratory or expiratory muscles. Moreover, a decrease in both inspiratory and expiratory muscle strength may not correlate with a general assessment of muscle strength. Primary muscle diseases like polymyositis cause more significant impairment of the respiratory muscles compared to the neuropathies. The relationship between inspiratory muscle strength and the onset of ventilatory insufficiency is not linear. Once maximum inspiratory mouth pressures decrease to less than 30% of that predicted, hypercapnia will usually ensue (Fig. 29-2).

**Lung and Chest Wall Mechanics**

Lung volume studies in patients with chronic respiratory muscle weakness often show a restrictive ventilatory pattern with a reduction in forced vital capacity (FVC) and preserved forced expiratory volume in 1 s/forced vital capacity ratio (FEV/FVC). Lung volume studies typically reveal a moderate reduction in total lung capacity and functional residual capacity with a normal or elevated residual capacity. A moderate fall in both inspiratory and expiratory reserve volume occurs. The decline in FVC is mainly caused by respiratory muscle weakness, and the decrease in FVC, in the absence of obstructive lung diseases, parallels the progression of the underlying respiratory muscle function. Thus, serial FVC measurement can be performed in the ICU setting to detect impending respiratory failure. However, a significant reduction in lung compliance may also contribute to decreased FVC in patients with chronic neuromuscular disease. The exact causes of reduced lung distensibility are unclear, but may be due to failed maturation of normal lung tissue in congenital

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Many patients with significant respiratory muscle dysfunction are asymptomatic.

Neuromyopathies may lead to different degrees of inspiratory and expiratory muscle weakness.

Respiratory failure ensues when maximum inspiratory pressure is <30% of predicted.

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**FIGURE 29-2**

In patients with neuromyopathies, the relationship of respiratory muscle strength (RMS) and PCO₂ is discontinuous. Hypercapnia is likely to occur only when respiratory muscle strength is less than 30% of predicted.
neuromuscular diseases, the presence of micro or macroatelectasis increases in alveolar surface tension caused by breathing chronically at low tidal volumes, and alterations in lung tissue elasticity.

Patients with neuromuscular disease have a rapid shallow breathing pattern similar to patients with interstitial lung disease. The exact mechanism of this abnormal breathing pattern is unclear and is thought to be caused by less compliant lungs and increases in lung elastic recoil. Similar to the changes seen in the lungs, a significant reduction in chest wall compliance is thought to be due to increased rib cage stiffness caused by chest wall fibrotic changes (i.e., tendons, ligaments, and costovertebral and costosternal articulations).

**Gas Exchange Abnormalities**

Hypercapnia and hypoxemia are late findings in patients with stable chronic neuromuscular disease. Hypercapnia with a relatively normal FVC and static maximum respiratory pressures should suggest sleep-related breathing disorders (obstructive sleep apnea, obesity hypoventilation syndrome), the presence of parenchymal lung diseases such as chronic obstructive airway disease, problems with central respiratory drive such as the chronic hypoventilation syndrome, or hypothyroidism (as previously discussed). Even if daytime gas exchange parameters are normal, significant hypoxemia and alveolar hypoventilation may occur during sleep, especially during REM sleep when the activity of the accessory respiratory muscles is diminished. In advanced chronic neuromuscular disease, evidence of alveolar hypoventilation on blood gas examination is likely when the FVC is less than 55% of that predicted and maximum inspiratory mouth pressure (PI\text{max}) and maximum expiratory mouth pressure (PE\text{max}) are less than –30 cmH\text{O} (Fig. 29-3). However, the onset of hypercapnia in advanced neuromuscular disease may be abrupt. Ventilation perfusion inequality due to atelectasis is the most common cause of hypoxemia in these patients.

**Effect of Neuromuscular Disease on Sleep**

Sleep-related breathing disorders such as impaired sleep quality and REM-related hypopnea are common in patients with respiratory muscle weakness caused by various neuromuscular diseases. Indeed, significant gas exchange abnormalities may be present and unsuspected even in the absence of daytime hypoxemia and hypercapnia.

Several physiologic changes occur in the respiratory system during sleep, particularly REM sleep, which can explain the predisposition of patients with poor pulmonary reserve in general, and respiratory muscle weakness in particular, to gas exchange abnormalities during sleep. Among the physiologic changes occurring during sleep are alveolar hypoventilation,

**FIGURE 29-3**

In patients with neuromyopathies, hypercapnia is likely to occur when the vital capacity (VC) is less than 55% of that predicted.
inhibition of accessory inspiratory muscle activity, and development of a chaotic breathing pattern during REM sleep that causes significant hypoventilation in patients with diaphragm weakness. In addition, pharyngeal muscle weakness, which is present in some neuromuscular diseases, may aggravate the physiologic loss of upper airway tone during REM sleep, thereby increasing the predisposition to obstructive sleep apnea and hypopnea.

If nocturnal hypoventilation is severe and remains clinically unrecognized, daytime hypercapnia and hypoxemia may ensue even in the absence of severe respiratory muscle dysfunction. Nocturnal gas exchange abnormalities usually precede and occur much earlier than abnormalities in daytime gas exchange. Indeed, patients with normal nocturnal gas exchange are unlikely to have abnormal daytime values.

Daytime gas exchange abnormalities and a decrease in FVC are useful in predicting patients with neuromuscular disease who are at risk for severe oxygen desaturation during sleep. In a study involving 20 patients with a variety of moderately advanced neuromuscular diseases, the degree of arterial oxygen desaturation during REM sleep was directly related to the severity of daytime hypercapnia and hypoxemia. Both percent predicted FVC and the decrease in FVC from the sitting to supine positions were also found to correlate with the minimum oxygen saturation measured during REM sleep. Mean decrease in FVC from the seated to the supine positions in this study was 21%. Interestingly, the maximum static respiratory pressures were not predictive of nocturnal hypoventilation.

Upper Airway Dysfunction

Upper airway dysfunction, manifested as the inability to handle oral secretions, recurrent aspiration, hoarseness, or stridor, is common in patients with neuromuscular dysfunction, especially when respiratory muscle weakness is present. Endotracheal intubation and mechanical ventilation are often required to protect the airway, prevent aspiration, and support ventilation once upper airway dysfunction becomes evident.

The flow–volume loop is useful in excluding significant upper airway dysfunction. Indeed, an abnormal flow–volume loop has a high sensitivity and specificity in predicting bulbar and upper airway involvement in patients with neuromuscular dysfunction. A typical flow–volume loop in a patient with motor neuron disease with bulbar involvement is shown in Figure 29-4. A sawtooth pattern of the flow loop contour has been described in patients with Parkinson’s disease. In addition, variable extrathoracic obstruction that reverses with drug therapy has been described in patients with myasthenia gravis.

The flow–volume loop is helpful in detecting upper airway dysfunction.

**FIGURE 29-4**
Upper airway obstruction caused by bulbar muscle involvement is common in patients with neuromuscular disease. The flow–volume loop may show a plateau of the inspiratory loop, suggesting extrathoracic upper airway obstruction.
EVALUATION OF PATIENTS WITH NEUROMUSCULAR DISEASE

Clinical History

The diagnosis of neuromuscular disease should be suspected in all patients who are admitted to the ICU with unexplained acute or chronic hypercapnic respiratory failure. Unless a high index of suspicion is used in the diagnosis of neuromyopathy, the diagnosis may be missed or delayed because the presence of neuromuscular dysfunction may be masked by the precipitating illness. Moreover, a detailed neurologic history is often not available in the ICU setting because patients may be intubated or are too breathless or confused to provide accurate information. In some cases, respiratory muscle weakness caused by a neuromuscular disease comes to light only after the patient has failed multiple weaning trials. Nevertheless, accurate historical details can often be obtained from family members, primary caregivers, and old medical records.

Inquiries about a preexisting neuromuscular disease are very important. Several neuromuscular diseases may cause sudden clinical deterioration, especially in advanced disease. Patients with congenital myopathies may develop cardiorespiratory failure or increased diaphragm weakness in the latter phases of their illness. The pattern of skeletal muscle weakness may suggest a particular diagnosis. Acute ascending paralysis of the lower extremities suggests Gullain–Barré syndrome; waxing and waning of neurologic symptoms are commonly seen in multiple sclerosis; and skeletal muscle weakness with repetitive action of a particular muscle group is highly suspicious of myasthenia gravis.

If possible, a detailed history of dietary intake over the last 48 h and drug and toxin ingestion should be obtained. Acute shellfish poisoning (saxatoxin) may lead to skeletal muscle weakness. A history of consumption of home-canned goods suggests botulinum toxin poisoning. Several commonly used drugs such as cholesterol-lowering agents, colchicine, cyclosporin, chloroquin, and l-tryptophan can cause myotoxicity.

Diseases that predominantly affect the pump function of the respiratory system (i.e., phrenic nerve injury) present as dyspnea on exertion, weak cough, and recurrent respiratory tract infections, whereas diseases that affect primarily the limb muscles (i.e., congenital myopathy, amyotrophic lateral sclerosis (ALS)) present as the inability to lift heavy objects, difficulty standing after sitting on a chair, or difficulty walking. However, some neuromuscular diseases such as ALS or mitochondrial myopathy can present initially as acute respiratory failure. Once the respiratory muscles are affected in advanced neuromuscular disease, respiratory failure may occur abruptly, due to an intercurrent illness, or slowly over months or years, finally culminating in hypercapnic respiratory failure. In most neuromuscular diseases, respiratory muscle weakness usually occurs insidiously and is typically associated with weakness of other skeletal muscle groups. However, up to 50% of patients with significant respiratory muscle weakness are asymptomatic until they develop respiratory failure.

Physical Examination

A thorough physical examination and a detailed neurologic assessment may reveal a previously undiagnosed neuromuscular disorder. However, physical examination may be limited...
by sedation, the use of neuromuscular blocking agents, or the presence of edema. Certain neurologic findings are helpful in differentiating upper motor neuron versus lower motor neuron lesions (Table 29-4) and in differentiating neuropathy versus myopathy (Table 29-5).

In patients with early or mild neuromuscular weakness, respiratory muscle weakness may not be detected on routine physical examination. Tachypnea at rest is very common with the onset of respiratory muscle weakness. As respiratory muscle weakness progresses, the increase in respiratory rate may be followed by signs of increasing respiratory distress such as nasal flaring, recruitment of the accessory muscles of respiration, and intercostal as well as subcostal retractions. Progressive weakness of the diaphragm eventually leads to paradoxical inward motion of the upper abdomen, often associated with rostral rib cage movement. Alternating paradoxical motions of the rib cage and abdomen indicates either high inspiratory elastic loads or impending respiratory failure. Indeed, paradoxical inward movement of the abdomen on inspiration that worsens with the recumbent position is typically seen in severe diaphragm weakness or paralysis.

**Ancillary Tests**

**Arterial Blood Gases**

Abnormalities in arterial blood gases (e.g., hypoxemia and hypercapnia) occur late in patients with severe respiratory muscle weakness and may not be present before the need to implement ventilatory support. Hypoxemia is commonly the result of microatelectasis due to ineffective cough and retained secretions, causing ventilation–perfusion mismatch or intrapulmonary shunting. More importantly, alveolar hypoventilation caused by respiratory muscle weakness or decreased central respiratory drive may also contribute significantly to hypoxemia. Hypoxemia caused by alveolar hypoventilation occurs due to reductions in PaO₂ that are proportional to elevations in PaCO₂, and as a result, the alveolar–arterial oxygen ...
gradient remains normal despite a lowered $\text{PaO}_2$. Pulse oximetry, which is a measure of
arterial oxyhemoglobin saturation, is useful in detecting hypoxemia, but is not a sensitive
indicator of hypventilation.

Hypercapnia is a late finding in severe respiratory muscle weakness. In fact, hypercapnia
does not occur until the respiratory muscle strength is less than 50% of that predicted. Careful
analysis of the pH and bicarbonate level is helpful in determining acute from chronic hyper-
capnic respiratory failure. Sleep-induced breathing disturbances may also lead to hypercar-
bia and should be carefully sought in susceptible patients.

**Pulmonary Function Tests**

Spirometry and lung volume studies are helpful in the initial evaluation as well as in follow-
up of patients with neuromuscular disease to determine the response to therapy. In general,
spirometry is hallmark by a restrictive pattern that is characterized by a reduction in FVC
and a normal FEV$_1$/FVC ratio. Moreover, there is a decrease in effort-dependent expiratory
flow such as peak expiratory airflow measurement, whereas FEV$_1$ and measurement of
midexpiratory flow rates (FEF$_{25-75}$ or FEF$_{50}$) are often greater than normal predicted values
because of increased elastic recoil. Increased elastic recoil pressure results from decreases in
both lung and chest wall compliance. Lung volume studies typically show a decrease in total
lung capacity (TLC) and an increase in residual volume (RV) due to expiratory muscle
weakness. Diffusion capacity is usually normal.

In the ICU setting, serial measurements of FVC are helpful in following the progression of
respiratory muscle weakness and in evaluating the need for partial or full ventilatory support.
In patients with rapidly progressive respiratory muscle weakness, as seen in Guillain–Barré
syndrome, daily measurement of FVC (<10 mL/kg or <1 L) helps to determine when to con-
sider elective airway intubation and institute mechanical ventilation. Alternatively, FVC can
also be used as one of the criteria for the initiation of weaning trials and liberation from
mechanical ventilation.

**Radiographic Assessment**

Radiographic findings in patients with neuromuscular disease are helpful in detecting pneu-
monia, atelectasis, and concomitant parenchymal lung disease. Although small lung vol-
umes on chest X-ray may suggest the possibility of inspiratory muscle weakness, this is a
very nonspecific finding in the ICU setting because portable chest X-rays are often used and
a film at maximum inspiration may not be obtained. Nevertheless, in the right clinical set-
ting, small lung volumes on chest radiograph and the presence of bilateral basal band-like
atelectasis suggest chronic volume loss that may be the result of weak respiratory muscles as
seen in bilateral hemidiaphragm paralysis. However, this radiographic picture could also be
easily dismissed as a poor inspiratory effort. On the other hand, unilateral hemidiaphragm
paralysis can be easily recognized on a routine chest radiograph as unilateral hemidiaphragm
elevation. The elevation of a hemidiaphragm due to weakness or paralysis can be confirmed
by performing a “sniff test” under fluoroscopy, which may demonstrate paradoxical upward
movement of the affected hemidiaphragm during a rapid sniff maneuver or lack of contrac-
tion during ultrasound imaging.

**Maximum Mouth Pressures**

Maximum static respiratory pressures, measured at the airway opening during a voluntary
contraction against an occluded airway, are the most sensitive tests to assess respiratory mus-
cle dysfunction in patients with neuromuscular disease even in the absence of symptoms and
normal ventilatory function. The extent of respiratory muscle weakness can be quantified by
measuring the maximum inspiratory ($P_{I\text{max}}$) and expiratory pressures ($P_{E\text{max}}$) that can be gen-
erated by the respiratory muscles. It should be remembered that the measurement of static
mouth pressures is affected by the underlying lung volume at which the test is performed.
Thus, $P_{I\text{max}}$ is measured near RV when the inspiratory muscles are at their greatest mechanical

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Hypoxemia and hypercapnia are late findings in patients with respiratory muscle weakness.

The usual pulmonary function test results in patients with respiratory muscle weakness are
decreased expiratory flow rates (FVC, FEV$_1$), increased RV, and decreased TLC.

Serial FVC measurement is a useful bedside test in predicting impending respiratory failure in
patients with rapidly progressive neuromyopathies.

Chest radiographic findings suggestive of respiratory muscle weakness are small lung vol-
umes, bilateral basal atelectasis, and elevated hemidiaphragm.

$P_{I\text{max}}$ and $P_{E\text{max}}$ are used to measure global inspiratory and expiratory muscle strength,
respectively.
advantage; PE\textsubscript{max} is measured near TLC when the inward recoil pressure of the respiratory system and the ability of the expiratory muscles to generate force are the greatest.

In chronic neuromuscular diseases, the measurement of both maximum static inspiratory pressures and expiratory pressures (P\textsubscript{I\textsubscript{max}} and P\textsubscript{E\textsubscript{max}}) is frequently decreased. Here, P\textsubscript{I\textsubscript{max}} and P\textsubscript{E\textsubscript{max}} usually range from 37 to 52% of normal depending on the type and severity of neuromuscular disease. In a study of 16 patients with various chronic neuromuscular diseases, the mean static inspiratory pressure measured by using an esophageal balloon was 43% of that predicted. In patients with proximal myopathies, hypercapnic respiratory failure has been reported to occur when P\textsubscript{I\textsubscript{max}} and P\textsubscript{E\textsubscript{max}} values were less than 30% or if the FVC was less than 55% of that predicted. Even in patients with only mild generalized muscle weakness, profound reductions in maximum static respiratory pressures may occur. In another study of 30 patients with stable chronic neuromuscular weakness, 30% of patients with relatively good general muscle strength had unsuspected severe respiratory muscle weakness (less than 50% predicted). Because of the frequent involvement of the respiratory muscles in neuromuscular diseases, the measurement of maximum static respiratory pressures should be routine in the assessment of neuromuscular disease patients, regardless of the severity or stage of the disease.

The P\textsubscript{I\textsubscript{max}} and P\textsubscript{E\textsubscript{max}}, in addition to FVC, are useful parameters to monitor the progression of respiratory muscle weakness in patients with acute neuromuscular disease, who are admitted to the ICU. These tests are reproducible, inexpensive, and easy to perform serially at the bedside to predict impending respiratory failure in patients with respiratory muscle weakness and the need for ventilatory support. Ventilatory support is often required when VC is less than 10–15 mL/kg or P\textsubscript{I\textsubscript{max}} is less than 20–25 cmH\textsubscript{2}O. In certain circumstances such as pneumonia, atelectasis, or the inability to clear secretions, mechanical ventilation may be required before these parameters are met.

Although measurement of maximum static respiratory pressures is useful in quantifying global respiratory muscle strength, it does not distinguish selective weakness of a particular respiratory muscle group and does not provide any information on respiratory muscle endurance. In contrast to maximum static pressures, which measure global respiratory parameters, transdiaphragmatic pressure (P\textsubscript{di}) specifically measures diaphragm strength. Although transdiaphragmatic pressure measurement is more invasive and not readily available in clinical practice, it may be useful when phrenic nerve injury is suspected, as can be seen following cardiac surgery or trauma.

**SPECIFIC NEUROMUSCULAR DISORDERS**

**Amyotrophic Lateral Sclerosis**

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of both upper and lower motor neurons leading to the loss of skeletal muscle function. The incidence of ALS is 1–2 per 100,000 people with peak incidence occurring between the ages 55–75. The majority of cases are sporadic (classical ALS), but 5–10% of cases result from autosomal dominant inheritance (familial ALS). There is a male predilection with a male to female ratio of 2:1. Death is usually the result of progressive respiratory failure and respiratory infections. Mean survival from the initial onset of symptoms is 3–4 years.

The exact etiology of ALS is unknown. A gene mutation located on chromosome 21q22 encoding copper–zinc superoxide dismutase, a free oxygen radical scavenger, has been identified in 10–15% of familial ALS patients. This finding suggests that the disease may be triggered by the susceptibility of the neurons to oxidative stress. Recent evidence suggests that the motor neurons are susceptible to glutamate-induced neurotoxicity. Glutamate is the principal excitatory neurotransmitter in the brain. The decreased uptake of glutamate is thought to lead to overstimulation of the glutamate receptors, which increases intracellular calcium. The increase in intracellular calcium activates proteolytic enzymes that cause cell membrane injury.

The usual clinical presentation in two-thirds of ALS patients is progressive weakness of the distal extremities, although early involvement of the bulbar muscles occurs in 25% of patients with ALS.
cases. Early involvement of the phrenic nerve motorneurons in some ALS patients can lead to acute respiratory failure or nocturnal hypoventilation even before clinical symptoms become apparent. Involvement of the upper airway and expiratory muscles can lead to abnormal swallowing and inadequate cough.

Although respiratory muscle impairment is usually evident only in advanced disease, abnormalities in pulmonary function tests may arise even in patients with only mild extremity weakness. Serial lung function studies in ALS patients invariably show a progressive reduction in FVC and maximum voluntary ventilation (MVV), as well as a progressive increase in residual volume (RV). The decline in FVC correlates with poor outcome. Both the maximum inspiratory (PIMax) and maximum expiratory pressures (PEmax) are reduced, to about 34 and 47% of predicted, respectively. In symptomatic patients with relatively preserved pulmonary function, MIP and MEP are frequently abnormal. An MIP of less than –60 cmH₂O is 100% sensitive for predicting less than 18-month survival.

The shape of the flow–volume curve may identify a subset of patients with greater weakness of the expiratory muscles. With severe weakness of the expiratory muscles, the flow–volume loop shows a concavity of the maximal expiratory curve with a sharp drop in flow at lower lung volumes. This group of ALS patients has lower maximal expiratory pressures, smaller vital capacities, and higher residual volumes compared to ALS patients with normal flow–volume loops.

Adequate oxygenation is usually well maintained even in those with severe abnormalities in spirometry. Monitoring the arterial blood gas is not useful in the early presentation of ALS. Spirometry, however, is still important in the initial evaluation of ALS patients because impairment in ventilatory function is frequently underestimated even by an experienced examiner.

The comprehensive management of the ALS patient should include measures to alleviate symptoms and evaluate the feasibility of specific drug therapy to alter its progressive clinical course. Riluzole, an antiglutamate drug, is FDA-approved for the treatment of ALS. Riluzole is the only treatment that has been shown to prolong survival in ALS or mechanical ventilation by approximately 3 months. It should be given to patients once a diagnosis of ALS is made. Therefore, despite optimal medical therapy, disease progression invariably occurs, resulting in respiratory insufficiency requiring some form of ventilatory assistance. The onset of respiratory failure often signals a rapid decline in global functional status as well. The need for mechanical ventilation should be discussed by the clinician with the patient and family early on in the disease course to prevent a rapid decline in the clinical symptoms of respiratory failure due to a rapid decline in lung function. In a survey of ALS patients, patients with early disease are more receptive to long-term ventilatory support compared to patients with advanced disease. ALS patients who develop respiratory symptoms, or who have a moderate reduction in lung function or a rapid decline in lung function, should be offered noninvasive positive pressure ventilation (NPPV) with techniques such as Biphasic (inspiratory and expiratory) positive airways pressure (BiPAP). In patients who can tolerate NPPV, the risk of death is decreased. In one study, 122 patients with ALS were offered BiPAP therapy once they developed dyspnea, or FVC less than 50%, or a fall of more than 15% in FVC in 3-month follow-up. Those patients who used BiPAP more than 4 h/day not only showed a slower decline in lung function, but also had decreased mortality rates.9

Some patients with acute respiratory decompensation may have a slight improvement in respiratory muscle strength after a period of ventilatory assistance. A randomized controlled trial assessed the effect of noninvasive mechanical ventilation versus standard care on survival and quality of life in a cohort of patients with ALS. Ninety-two patients were randomly assigned to noninvasive ventilation or standard care when they developed orthopnea with MIP of <60% or in the presence of hypercarbia. NPPV improved survival and improved the quality of life in patients with no bulbar, or at most, only mild bulbar symptoms.10 In patients with severe bulbar symptoms, NPPV only improved the quality of life. In the ICU setting, NPPV should be tried first in ALS patients who experience acute-on-chronic respiratory insufficiency especially in the absence of significant bulbar symptoms. Patients with significant bulbar symptoms usually cannot tolerate NPPV because of difficulty handling oral secretions. Theophylline may improve respiratory muscle strength and can be used in the absence of adverse effects.
of tachyarrhythmias. In patients with ALS, theophylline improved the negative inspiratory pressure, FVC, and peak inspiratory flow by 28%, 10%, and 12%, respectively.\(^{11}\)

**Phrenic Nerve Injury**

Unilateral or bilateral diaphragm weakness can follow phrenic nerve injury. Reported causes of phrenic nerve injury are listed in Table 29-6. In most cases of diaphragm weakness, the exact diagnosis remains elusive. In diaphragm dysfunction following cardiac surgery, phrenic nerve injury occurs secondary to cold exposure and/or to mechanical stretching during surgery.

The diagnosis of bilateral diaphragm weakness is often delayed. The symptoms of diaphragm weakness are often nonspecific, and the routine physical findings are insensitive and unreliable. In the absence of parenchymal lung disease or heart failure, dyspnea that is made worse by lying down is an important clue to the diagnosis. The cephalad displacement of the abdominal contents in the supine position further increases the workload of the already weakened diaphragm. Significant diaphragmatic weakness can often be confirmed during physical examination by the presence of thoracoabdominal paradox in the recumbent position and the use of accessory muscles of respiration during tidal breathing.

Unilateral diaphragm weakness, in contrast, is usually well tolerated even if the pulmonary function test (PFT) reveals a mild reduction in FVC and TLC. The diagnosis of unilateral diaphragm weakness is often suspected only after review of a chest radiograph that was ordered for another clinical indication. Extensive workup is usually not warranted unless severe symptoms are present.

Once the diagnosis of diaphragm weakness is clinically suspected, measurement of respiratory muscle strength and fluoroscopic findings on the sniff test may confirm the diagnosis. On routine pulmonary function testing, bilateral diaphragm paralysis reveals a restrictive ventilatory defect characterized by a decrease in FVC, RV, and TLC. The VC is typically reduced to less than 50% of that predicted in the erect posture and is further reduced in the recumbent posture. In the upright posture, contraction of the abdominal muscles during expiration and relaxation during early inspiration results in an outward motion of the abdomen and facilitates passive descent of the diaphragm. In the recumbent posture, diaphragm function is further impaired by the increase in the inspiratory workload imposed by cephalad displacement of the abdominal viscera. As in any other neuromuscular disease, chronic hypercapnic respiratory failure may be seen in moderate-to-severe bilateral diaphragm weakness.

Radiographic findings in patients with diaphragm weakness typically show either unilateral or bilateral elevation of the diaphragm, depending on the location of the phrenic nerve injury. However, parenchyma and pleural diseases such as atelectasis, pulmonary fibrosis, subpulmonic fluid collections, or atelectasis may also show the same radiographic picture. A fluoroscopic technique to evaluate diaphragmatic excursion known as the sniff test is helpful to further evaluate the presence of diaphragm paralysis. As described earlier, the paralyzed diaphragm exhibits an upward paradoxical movement into the chest cavity because of the development of negative intrapleural pressures during the sniff maneuver. The sniff test is not useful in the evaluation of bilateral diaphragm paralysis and may result in an apparently false-normal study. A false negative test may result when both hemidiaphragms appear to descend normally during a sniff maneuver, despite profound weakness, due to a sudden relaxation of the abdominal muscles (i.e., passive inspiration). In addition, a positive sniff test should also be interpreted with caution because this can be seen in up to 6% of normal

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**TABLE 29-6**

**CAUSES OF PHRENIC NERVE INJURY**

| Thoracic surgery | Motor neuron disease |
|------------------|----------------------|
| Chest trauma     | Myopathies           |
| Mediastinal tumors | Neuropathies         |
| Mediastinal and pleural infection | Myelopathies |
| Forceful neck manipulation | |
individuals. Paradoxical diaphragm movement should be at least 2 cm to increase the test’s specificity.

The measurement of transdiaphragmatic pressure ($P_d$), despite its limitations discussed earlier (e.g., intersubject variability, invasive procedure, need for full patient cooperation), is useful in the diagnosis and quantitation of diaphragm weakness. Total diaphragm paralysis is diagnosed when there is no pressure difference measured across both sides of the diaphragm ($P_d = 0$) during a forced inspiratory maneuver against an occluded airway.

The recovery of diaphragm weakness depends on the etiology. In phrenic nerve injury following cardiac surgery, 80% of patients recover nerve function in 6 months and 90% in 1 year.

**Guillain–Barré Syndrome**

Guillain–Barré syndrome (GBS) is a form of acute demyelinating inflammatory polyneuropathy that usually presents clinically as a rapidly ascending, symmetrical paralysis of the lower extremities, loss of tendon reflexes, mild or absent sensory signs, and autonomic dysfunctions. Involvement of the bulbar and respiratory muscles may lead to swallowing dysfunction, increased risk of aspiration, and respiratory failure. Although the exact etiology is unknown, in approximately 70% of cases an antecedent viral or bacterial infection, 1–4 weeks prior to presentation, can be identified from the history. The current concept suggests that GBS is a self-limited, reactive autoimmune disease in which an aberrant immune response is directed against bacterial lipopolysaccharides that share similar epitopes with the myelin sheath or Schwann cell basement membrane. Viral infections associated with GBS include Cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, and Varicella-zoster virus. Cytomegalovirus is the most frequently identified viral infection; it has been documented to precede GBS in 11–22% of cases. In such cases, serologic testing may reveal positive anti-CMV immunoglobulin M (IgM) antibody, high serum antibody titers to GM2 gangliosides or to sulfated glycolipids of peripheral myelin. GBS associated with CMV infections has the predilection to affect female and younger patients, and is commonly associated with facial and bulbar palsies, respiratory failure, and severe sensory loss. Campylobacter jejuni is the most frequent bacterial infection preceding the diagnosis of GBS. In 23–45% of sporadic cases of GBS, recent C. jejuni infections can be documented by serologic testing or bacterial culture. The actual risk of developing GBS following C. jejuni is 1 in 1,000, suggesting that host susceptibility plays an important role in the pathogenesis of GBS. Unlike GBS preceded by CMV infection, C. jejuni associated GBS often presents as pure motor axonal neuropathy, and seldom involves the cranial nerves. However, it can present as Miller-Fisher syndrome characterized by ophthalmoplegia, ataxia, and areflexia. Serum from such patients often contains high titers of antibodies against gangliosides. High serum GQ1b titer is considered pathognomonic of Miller-Fisher syndrome. Mycoplasma pneumoniae infection is the second most common cause of bacterial infection linked to GBS occurring in approximately 5% of GBS cases. Some cases of GBS have been linked to influenza vaccination, recent surgery, trauma, and malignancy (lymphoma).

The clinical signs and symptoms of GBS are shown in Table 29-7. The symptoms typically begin with a sensory phase consisting of numbness and tingling in the fingers, toes, and trunk lasting 7–10 days. Pain over the extremities or flank is commonly reported as a “charley horse,” but objective sensory impairment is minimal despite complaints of paresthesias. This stage is classically followed by an ascending pattern of limb weakness progressing from the lower to upper extremities. The extent of motor weakness is variable, ranging from mild paresis to complete paralysis. In 50% of GBS cases, weakness of the lower extremities usually peaks within several days of diagnosis. The muscle weakness usually does not progress beyond 4 weeks. Autoimmune dysfunction is very common. Other variants of Guillain–Barré syndrome with asymmetric involvement of the extremities, presence of ataxia, or the absence of paresthesias have been described. It is important to recognize the Miller–Fisher syndrome (ophthalmoplegia, ataxia, and areflexia), variant of GBS.

Abnormal CSF examinations and nerve conduction studies are confirmatory for the diagnosis of Guillain–Barré syndrome. Cerebrospinal fluid (CSF) examination characteristically
Initial laboratory examination showed a normal hemogram and routine blood chemistries. Cerebrospinal fluid examination revealed WBC of 4/mm³, RBC of 0/mm³, glucose of 55 mg/dL, and protein of 96 mg/dL. EMGs of both lower and upper extremities showed prolonged sensory and motor latencies with decreased conduction velocities. A diagnosis of Guillain–Barré syndrome was made. The patient was admitted to the neurology service and was immediately started on intravenous immunoglobulin. On admission, his FVC was 2.8 L and his PI_max was 110 cmH₂O. An arterial blood gas showed a pH of 7.39, PaCO₂ of 42 mmHg, PaO₂ of 80 mmHg, and a HCO₃⁻ of 24 mEq/dL. He appeared comfortable, and denied shortness of breath. On the third hospital day, he complained of shortness of breath after going to the bathroom. A repeat FVC was 2.0 L, a notable decrease compared to admission. He was transferred to the ICU.

shows increased CFS fluid protein with a cell count of less than 10 mononuclear leukocytes per cubic millimeter. This CFS finding is commonly referred to as albuminocytologic dissociation. A cerebrospinal spinal fluid cell count of greater than 50 mononuclear cells per cubic millimeter may indicate an associated HIV infection. Other abnormalities include elevated liver enzymes that are observed in 40% of the patients. Because of increased secretion of antidiuretic hormone, hyponatremia is detected in 25% of patients. The clinical significance of the presence of specific antigangliosides is uncertain and routine assessment is not recommended since their presence has no impact on therapy. Nerve conduction studies typically show multifocal demyelination. Slowing of nerve conductions and a partial or complete block of conduction in motor fibers are the cardinal electrophysiologic findings. In later stages of the disease, the signs of axonal degeneration are suggested by reduced amplitudes of motor and sensory compounds’ action potentials. The proposed diagnostic criteria for typical Guillain–Barré syndrome are shown in Table 29-8.

Acute respiratory failure is one of the well-recognized complications of GBS. In 15–30% of cases of GBS, acute respiratory failure is profound and requires mechanical ventilation. The incidence of acute respiratory failure increases by twofold once respiratory muscle dysfunction is detected and the patient requires ICU care. Other common complications are pneumonia, recurrent aspiration, and pulmonary thromboembolic disease.

All patients suspected of having GBS and showing signs of respiratory muscle dysfunction should be transferred to the ICU for closer monitoring. Other clinical indications for admission to the ICU are listed in Table 29-9. Severe weakness of diaphragm force-generating capacity is shown by a marked reduction in maximum transdiaphragmatic pressures during acute ventilatory failure and early recovery from the illness. Serial FVC is the most useful test in predicting the need for mechanical ventilation and should be performed once or twice daily depending on the clinical condition of the patient. Figure 29-5 shows the changes in respiratory function with the progressive decline in FVC and its suggested treatment. Several studies have shown that a FVC of 12–15 mg/kg is a sign of imminent respiratory failure. In patients

| SYMPTOMS | INCIDENCE(%) |
|----------|--------------|
| Ascending paralysis of the lower extremities | 95 |
| Paresthesias | 85 |
| Facial muscle weakness | 60 |
| Oropharyngeal muscle weakness | 50 |
| Orbicular muscle weakness | 15 |
| Autonomic dysfunction | 65 |
| Cardiac arrhythmia | Blood pressure lability |
| Gastrointestinal dysfunction | Pupillary dysfunction |
| Sweating abnormalities | Urinary retention |

| USUAL CLINICAL SIGNS AND SYMPTOMS OF GUILLAIN–BARRÉ SYNDROME |
|-------------------------------------------------------------|
| Acute respiratory failure occurs in 15–30% of GBS patients. |

Indications for ventilatory support in GBS include FVC < 12–15 mL/kg, upper airway dysfunction, and hypoxemia and hypercapnia.
who develop respiratory failure due to Guillain–Barré syndrome, FVC measured serially decreased from a mean of 2.5–0.9 L within 2 weeks. In a recent study of 81 GBS patients who required mechanical ventilation, the average FVC at the time of intubation was $33 \pm 11\%$.

Other indications for intubation and ventilatory support include respiratory distress, inability to handle oral secretions, hypoxemia ($\text{PaO}_2 < 70$ mmHg on room air or alveolar–arterial $\text{O}_2$ difference $>300$ mmHg while inspiring $100\%$ oxygen), and hypercapnia. Blood gas analysis is used to ensure adequate oxygenation and ventilation. Hypercapnia is a late sign of ventilatory failure and should not be relied upon as an indication for when to start mechanical ventilation. The average $\text{PaCO}_2$ at the time of intubation when FVC is less than 12 ml/kg was 43 mmHg in two large series of GBS patients. Other predictors of the need for mechanical ventilation include time between onset of disease and hospital admission of $\leq 7$ days, inability to lift head, presence of bulbar dysfunction, and the presence of anti-GQ1b antibodies. A recent study suggests that neurophysiological testing is helpful in predicting the need for mechanical ventilation. Of the 154 patients included in this study, patients with the demyelinating form of GBS required mechanical ventilation more often than patients with axonal or equivocal findings on electrophysiology. The risk of acute respiratory failure was only 2.5% if the proximal/distal compound muscular amplitude potential (p/dCMAP) ratio was $>55.6\%$ and a forced vital capacity was $>81\%$.

| TABLE 29-8 |
| Features required for diagnosis | Progressive weakness of both upper and lower extremities |
| Features strongly supporting the diagnosis | Areflexia |
| | Progression of symptoms over days to 4 weeks |
| | Symmetry of symptoms |
| | Mild sensory symptoms or signs |
| | Cranial nerve involvement, especially bilateral weakness of facial muscles |
| | Recovery beginning 2–4 weeks after progression ceases |
| | Autonomic dysfunction |
| | Absence of fever at the onset |
| | Elevated protein concentration in CSF with fewer than 10 cells/ml³ |
| Features making the diagnosis doubtful | Typical electrodagnostic features |
| | Sensory level |
| Features excluding the diagnosis | Diagnosis of botulism, myasthenia, poliomyelitis, or toxic neuropathy |
| | Abnormal porphyrin metabolism |
| | Recent diphtheria |
| | Purely sensory syndrome without weakness |

| TABLE 29-9 |
| CLINICAL INDICATIONS FOR ADMISSION TO THE ICU IN PATIENTS WITH GUILLAIN–BARRÉ SYNDROME |
| C | Conduction block, bradycardia, asystole |
| R | Rapid progression of motor weakness |
| I | Infection |
| T | Tachyarrhythmias |
| I | Intensive care monitoring of respiratory and autonomic dysfunction |
| C | Complications of critical illness: pulmonary embolism, myocardial infarction |
| A | Airway: ventilatory failure, bulbar weakness |
| L | Labile blood pressure: hypertension/hypotension |

The word “critical” is used as a mnemonic for the different indications.
In the ICU, the patient was started on subcutaneous heparin for prophylaxis against deep venous thrombosis. Daily range-of-motion exercises were also performed to prevent the development of limb contractures. Over the next 2 days in the ICU, the patient’s FVC decreased further, to 1.5–1.6 L (weight, 100 kg). In addition, his limb weakness continued to worsen despite repeated plasma infusions. He was now unable to get out of the bed without nursing assistance. His chest x-ray showed bibasilar atelectasis and mild pulmonary vascular congestion. Because of his continued clinical deterioration and chest radiographic findings of fluid overload, the plasma infusion was stopped and plasmapheresis was initiated. On the third hospital day, he was noted to have a nasal voice and complained of difficulty in swallowing liquids. A repeat arterial blood gas showed a pH of 7.35, PaCO₂ of 45 mmHg, PaO₂ of 70 mmHg, and HCO₃ of 22 mEq/dL. He was electively intubated and placed on mechanical ventilation.

Upper airway dysfunction due to bulbar muscle dysfunction in GBS may cause inability to swallow oral secretions and increase the risk for pulmonary aspiration. Clinical signs of bulbar muscle dysfunction such as a nasal voice, abnormal gag reflex, dysarthria, and poor mobility of pharyngeal muscles must be sought frequently. In addition, swallowing dysfunction can be assessed at the bedside by asking the patient to drink sips of water and observe for the temporal occurrence of coughing. Early intubation may be necessary to protect the airway even if respiratory muscle strength is still adequate. A recent study suggested that delaying intubation may increase the risk of early onset of pneumonia.⁰¹⁵

Weaning may be started once FVC exceeds 8–10 mL/kg, adequate oxygenation is achieved with a FiO₂ of 40% or less, and patients are able to double their minute ventilation. The maximum negative inspiratory force at the time of successful weaning is usually greater than 40 cmH₂O. The average duration of mechanical ventilation in two large series was 50–55 days.¹³ Some patients may require tracheostomy because of the need for prolonged mechanical ventilation and pulmonary toilet. In patients who have shown a favorable
response to treatment, tracheostomy may be delayed for up to 10 days in an attempt to avoid
the procedure in patients who rapidly improve.

Aggressive pulmonary toilet is indicated to prevent as well as treat atelectasis. Atelectasis
may require repeated bronchoscopy and may decrease the incidence of nosocomial pneumo-
nia. Bulbar involvement increases the risk of aspiration pneumonia. In a study of 81 GBS
patients who required mechanical ventilation, 78% developed pneumonia that was largely
attributed to aspiration.15 Subcutaneous heparin is the preferred therapy for deep venous
thrombosis prophylaxis when compared to pneumatic boots, which may lead to prolonged
foot drop secondary to compression of the peroneal nerve.

Autonomic dysfunction can occur in 65% of patients with GBS. Common manifestations
of autonomic dysfunction include labile blood pressure, sinus tachycardia, excessive sweat-
ing, urinary retention, and ileus. Autonomic dysfunction is commonly prevalent in patients
who required mechanical ventilation and during the progressive and plateau phases of the
illness. Particular care should be observed during endotracheal suctioning since it can pre-
cipitate tachy and brady-arrhythmias and even asystole from vagal stimulation. Moreover,
patients may be overly sensitive to vasoactive medications. Management of severe ileus
includes bowel rest and therapeutic trials with erythromycin or neostigmine. The use of
promotility agents is contraindicated in patients with dysautonomia.

Immune modulation using either plasma exchange or intravenous immune globulin infu-
sion is the mainstay of therapy in GBS.20-23 In two multicenter trials,21,22 plasmapheresis
using either albumin or fresh-frozen plasma (50 mL/kg, given on five separate occasions in
course of 2 weeks) as replacement fluids showed short-term benefits in early motor recovery
and ambulation, reduced the number of patients who required assisted ventilation, and short-
ened the duration of mechanical ventilation. Immunotherapy should be started within 2
weeks of the onset of symptoms or as early as possible. However, in patients with rapidly
deteriorating clinical symptoms, plasmapheresis may still offer some benefits even if the
duration of the disease is greater than 3 weeks. In approximately 10% of patients, relapse of
neurologic symptoms may follow plasma exchange treatment due to antibody rebound. In
such circumstances, additional plasma exchange treatment or intravenous immunoglobulin
treatment is helpful. Intravenous immunoglobulin (IVIG) (usually given at a dose of 2 g/kg
divided over 2–5 days) given within 2 weeks is as effective as plasma exchange therapy.
Since IVIG is easier to administer, it is preferred over plasma exchange unless there are
specific contraindications to its use such as low serum immunoglobulin, a presence of uncon-
trolled hypertension, and a hyperosmolar state. There is no additional benefit conferred by
sequential treatment, consisting initially of plasmapheresis followed by IVIG, when com-
pared to either treatment alone.24 Corticosteroids alone confer no therapeutic benefit and
may slow recovery in GBS; it is not recommended.25 The combination of IVIG and intrave-
nous methylprednisolone may hasten recovery, but there has been no documented beneficial
effect on the long-term outcome.

With the advent of modern ICU care, mortality from GBS has decreased from 15% in the
1970s to 3–4% in the 1980s. Prognosis is good, but a minority of patients will have no neu-
rologic residual; 50–65% of patients will have persistent mild neurologic dysfunction such
as mild distal weakness or numbness. Factors associated with poor prognosis are age greater
than 60 years, mean compound muscle action potential amplitudes from distal stimulation
less than 20% of normal, need for ventilatory support, and rapid progression to severe weak-
ness (less than 1 week).

CASE STUDY: PART 5
On the sixth ICU day, the patient showed signs of motor strength
recovery. Both hip and knee flexion and extension were 4/5.
Similar increases in muscle strength were observed in his upper
extremities. Weaning parameters showed FVC of 2.2 L, maximum
negative inspiratory pressure of 38 cmH₂O, and a minute ventila-
tion of 6 L/min. He was successfully extubated after 2 h of a
T-piece weaning trial. He was transferred from the ICU the follow-
ing day without further incident.

**Factors that are associated with a poor prognosis in GBS include:**
- Older age
- Mean compound muscle action potential amplitudes < 20%
- Need for ventilatory support
- Rapid progression of symptoms
Critical Illness Polyneuropathy and Neuromyopathy

Critical illness polyneuromyopathy (CIPNM) is the most common cause of acquired neuromuscular weakness in both surgical and medical ICU patients. The incidence of CIPNM depends on the severity of illness, the diagnostic criteria used, and the timing of examination from the onset of the critical illness. In prospective studies, 25–63% of patients who required mechanical ventilation for at least 7 days developed CIPNM. Patients with sepsis and sepsis syndrome have the highest incidence of CIPNM and it approaches 70–100%. Axonal polyneuropathy was initially thought to be the main pathologic changes in ICU-acquired weakness. However, electromyography (EMG) and muscle biopsy studies showed that acute myopathy coexists with polyneuropathy, and in fact, often exists as separate clinical entity. Accordingly, CIPNM is divided into four categories, namely critical illness myopathy, critical illness polyneuropathy, neuromuscular junction abnormalities, and combined polyneuromyopathy (Table 29-10). In a prospective study of 30 patients with critical illness polyneuropathy, biopsy of the quadriceps femoral muscle showed neuropathic changes in 37%, myopathy in 40%, and both neuropathic and myopathic changes in 23% of patients. Muscle necrosis was also present in 30% of the muscle biopsies specimen.

Several risk factors commonly encountered in the ICU setting have been identified in the development of CIPNM. These include severe systemic inflammation especially due to sepsis, sepsis syndrome, multisystem organ failure, use of corticosteroids and neuromuscular blocking agents, hyperglycemia and hyperosmolality, immobility, use of aminoglycosides, and duration of mechanical ventilation. Indices that measure the severity of critical illness, such as the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) III, or the Sequential Organ Failure Assessment Score (SOFA), are also important predictors of the occurrence of CIPNM. The detrimental effect of hyperglycemia on neuromuscular function is supported by a recent study showing that intensive insulin therapy to maintain normoglycemia (blood glucose levels between 80 and 110 mg/dL) decreases the incidence of critical illness polyneuropathy by 44% compared to conventional insulin therapy (blood glucose level between 180 and 200 mg/dL). In addition, the cases of CIPNM in the intensive insulin treatment group resolved faster. The risk of CIPNM was linearly correlated with the mean blood glucose level. In multivariate analysis, independent predictors of polyneuropathy include conventional insulin treatment (odds ratio 2.6; 95% confidence interval 1.6–4.2), vasopressor support of more than 3 days (odds ratio 2.5; 95% confidence interval 1.4–4.2), bacteremia (odds ratio 2.0, 95% confidence interval 1.3–3.8), and dialysis (odds ratio 1.9, 95% confidence interval 1.0–3.8). Similarly, intensive insulin therapy decreased the incidence of CIPNM in patients who required mechanical ventilation for more than 7 days in the medical ICU compared to conventional treatment with an absolute risk reduction of 11.6%. Moreover, the cumulative risk of CIPNM over time was also significantly reduced in patients who received ventilatory support, partially explaining the decrease in the duration of mechanical ventilation.

The pathogenesis of CIPNM is not well understood. Since the systemic inflammatory response and multisystem organ failure almost always precedes CIPNM, an exaggerated immune response to injury is thought to be the main pathogenic pathway leading to nerve and muscle injury. The resulting unmitigated systemic and local inflammatory response, in

### Table 29-10

| Myopathy              | Acute necrotizing myopathy |
|-----------------------|---------------------------|
| Cachectic             |                           |
| Acute rhabdomyolysis  | Thick filament (myosin)   |
| Loss                  |                           |
| Neuromuscular junction abnormalities | Myasthenia-like syndrome |
| Neuropathy            | Prolonged neuromuscular blockade |
| Neuropathy            | Critical illness           |
| Polyneuropathy        |                           |
| Acute motor neuropathy|                           |
| Polyneuromyopathy     | Combination of neuropathy and myopathy |

Insulin therapy to control hyperglycemia to euglycemic levels can decrease the risk of critical illness polyneuropathy.

Sepsis and multisystem organ failure are the two most common causes of acquired muscle weakness syndrome in the ICU.

Axonal degeneration of the motor and sensory nerves, loss of muscle contractile (myosin) proteins, and muscle membrane inexcitability are the pathophysiologic changes in CIPNM.
particular, the release of tumor necrosis factor alpha, interleukin 1 and 12, and the recruitment of T-helper 1 cells, monocyte, macrophages, and neutrophils, leads to endothelial cell injury. This causes increased microvascular permeability and endothelial edema that decreases blood flow to the nerve and muscle tissue. The end result of this inflammatory cascade is primary axonal degeneration of the sensory and motor fibers and muscle atrophy with loss of contractile proteins and membrane inexcitability. An animal model of sepsis showed that sepsis triggers enhanced muscle protein proteolysis through the ubiquitin-proteosome and calpain system causing myofibrillar degradation and disruption of the sarcomere. Recent studies suggest that critical illness myopathy is not only due to selective myosin loss, but also due to muscle fiber membrane electrical inexcitability caused by defective sodium channel regulation. Animal models of critical illness myopathy reveal altered membrane expression and function of the sodium channels.37

The syndrome is often initially suspected because of distal symmetrical muscle weakness seen after 5–7 days of mechanical ventilation in awake patients, or in those patients who are difficult to wean from mechanical ventilation. These patients usually have no prior history of neuropathy or myopathy. The muscle weakness is most prominent in the lower extremities and is accompanied by muscle wasting and reduced or absent tendon reflexes. Facial muscle weakness, presence of asymmetrical weakness of the limb, or pyramidal signs should prompt further workup to rule out other neurologic causes of weakness. Assessment of peripheral muscle strength can be difficult because of sedation, delirium, or the presence of metabolic encephalopathy. Nevertheless, if motor strength assessment is possible, a standardized muscle examination can be used to assess the degree of weakness in individual muscle groups. The Medical Research Council (MRC) Scale for muscle examination includes strength assessment of three different muscle groups on each limb and ranks them on a scale from 0 to 5 as seen in Table 29-11.23 The MRC score is easy to use, and reproducible even in mechanical ventilated patients. Three muscle functions are evaluated in the upper and lower limbs. Each function score ranges from 0, which denotes no detectable movement, to 5 denoting normal power. The total score ranges from 0 to 60. A score of less than 48 reflects significant weakness.

The diagnosis of CINM can often be made based on typical clinical presentation. Nerve conduction studies and electromyography are useful in detecting the presence of sensorimotor axonal polyneuropathy and associated myopathy. In axonal polyneuropathy, ENMG testing shows a reduction in the amplitude of the compound action potential with normal conduction velocity on motor nerve stimulation, and spontaneous electrical activity on muscle needle recording. This EMG pattern can be seen in 70–100% of ICU with severe sepsis and after 5–7 days of mechanical ventilation. A myopathic pattern on ENMG is suggested by the presence of a prolonged compound muscle action potential and a short duration and low amplitudes of motor unit potentials on voluntary activation. Creatine phosphokinase levels (CPK) are either normal or slightly elevated in CIPNM. Muscle and nerve biopsy can be used to confirm the diagnosis, but are not routinely indicated. Muscle biopsy usually

Critical illness polyneuropathy should be suspected in patients who fail weaning from mechanical support, develop areflexic limbs weakness, or have a complicated ICU course as a result of sepsis.

Symmetrical muscle weakness without facial weakness in an awake patient who has been on mechanical ventilation for more than a week is a common clinical presentation of CIPNM.

Electrodiagnostic testing is useful in confirming the diagnosis of CIPNM, and in detecting the presence of combined myopathy and polyneuropathy. Muscle necrosis and atrophy of type 1 muscle fibers are commonly seen on muscle biopsy.

EMG is the ancillary test of choice to confirm the diagnosis of critical care polyneuropathy and to exclude other causes of weakness. The EMG finding in critical illness polyneuropathy (CIP) is primary axonal polyneuropathy.

**TABLE 29-11**

**MRC SCALE FOR MUSCLE EXAMINATION**

| Functions assessed | Score for each movement |
|--------------------|-------------------------|
| Upper extremity: wrist flexion, forearm flexion, shoulder abduction | 0 – No visible contraction |
| Lower extremity: ankle dorsiflexion, knee extension, hip flexion | 1 – Visible muscle contraction, but no limb movement |
| | 2 – Active movement – but not against gravity |
| | 3 – Active movement against gravity |
| | 4 – Active movement against gravity and resistance |
| | 5 – Active movement against full resistance |
| Maximum score: 60 (four limbs, maximum of 15 points per limb) | Minimum score: 0 (quadriplegia) |

Source: Data from Kleyweg et al.23
shows type II fiber atrophy and occasionally type I atrophy and muscle necrosis. Immunohistochemistry and electron microscopy show a loss of myosin thick filaments. In the right clinical setting, extensive neurologic testing or biopsy of the nerve or muscle are not required to make a confident diagnosis of CIPNM. A diagnostic algorithm for the diagnosis of ICU-acquired weakness is shown in Figure 29-6.

The differential diagnosis of muscle weakness in the ICU setting encompasses multiple central nervous system pathologies, including head and spinal cord injury. In acute spinal injury, spinal shock may cause quadriparesis and areflexia mimicking polyneuropathy. Muscle weakness associated with ptosis and bulbar weakness suggest neuromuscular junction diseases such as myasthenia gravis. Axonal variants of the Guillain–Barré Syndrome are distinguished by the presence of weakness before admission to the ICU, a preceding history of Campylobacter jejuni infection and positive serologic test for anti-GM1 or anti-GD1a antibodies. Prolonged use of neuromuscular blocking agents, especially in the presence of hepatic and renal failure, can lead to persistent neuromuscular blockade due to delayed clearance of the drugs (see Chap. 58).

Since there is no specific treatment for CIPNM, avoidance of recognized risk factors is important in decreasing the incidence and morbidity and mortality associated with this disease process. Preventive measures include tight blood glucose control, avoidance or minimization of corticosteroids and/or neuromuscular blocking agents, early mobilization and

Primary neurologic diseases that can mimic CIPNM include acute spinal injury, myasthenia gravis, axonal variants of Guillain–Barré syndrome, and prolonged neuromuscular blockade due to delayed clearance of neuromuscular agents.

ICU management strategies that may decrease the risk of CIPNM include tight blood sugar control, minimization of corticosteroids and/or neuromuscular blocking agents, early physical therapy, and daily interruption of sedation.
Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by impaired transmission of neural impulses across the neuromuscular junction due to the destruction of the postsynaptic acetylcholine receptors. It is the most common neuromuscular transmission disorder with an estimated incidence of 10–20 cases per million people and a prevalence of 100–200 per million. In the U.S., approximately 18,000 people are affected. Younger women of childbearing age are affected twice as frequently as men. Thymic tumors are seen in 10% of cases, mostly in older men.

The disease is recognized clinically as fluctuating weakness of the ocular, bulbar, limb, and respiratory muscles. The most common clinical presentation in 50% of the patients is weakness in extraocular muscles manifesting initially as ptosis and diplopia. This is recognized as the ocular form of the disease. In the generalized form of the disease, variable involvement of bulbar, limb, and respiratory muscles also occurs. Bulbar muscle weaknesses such as dysarthria, dysphagia, and fatigable chewing are the initial presenting symptoms in 15% of cases. Approximately 50–60% of patients with the ocular form of the disease develop generalized weakness involving the oropharyngeal muscles, diaphragm, other respiratory muscles, and limbs, within the first 2 years of the onset of symptoms. Respiratory muscle weakness is seen in one third of patients and may occur in the absence of peripheral muscle weakness. On physical examination, fatigability of the involved muscles can be elicited by asking the patient to do repetitive or sustained muscle activity such as looking upward for several minutes elicits lid or ocular muscle weakness.

The Tensilon test is a simple test that can be done at the bedside to confirm the diagnosis of myasthenia gravis. Tensilon (edrophonium) is a short-acting inhibitor of acetylcholinesterase and can be given intravenously to elicit a transient improvement in muscle weakness. A positive Tensilon test highly suggests myasthenia gravis, but a positive test has also been reported in patients with Lambert–Eaton syndrome, botulism, and ALS. In patients with moderately generalized myasthenia gravis, pulmonary function testing reveals a mild reduction in FVC and a moderate reduction in both inspiratory and expiratory strength, indicating respiratory muscle weakness. Treatment with pyridostigmine, both available in IV and tablet formulation, may improve FVC, MIP, and MEP, although respiratory muscle strength does not normalize. As in other chronic neuromuscular diseases, the breathing pattern is rapid and shallow. Arterial blood gas examination is frequently normal even with severe impairment of transdiaphragmatic pressures ($P_{D}$). Arterial blood gases are, therefore, not useful in monitoring the severity of respiratory muscle dysfunction.

A serologic test may also be used to support the diagnosis of myasthenia gravis. Antibodies to acetylcholine receptors are seen in 80% of patients with generalized myasthenia and 60% with ocular myasthenia. The concentration of the acetylcholine receptor antibodies does not correlate with the severity of disease. Acetylcholine receptor antibodies have been found in Lambert–Eaton syndrome and in systemic lupus erythematosus. Recent studies showed that the presence of antimuscle specific kinase (MuSK) antibodies identifies a subgroup of
patients with myasthenia gravis who have a higher incidence of bulbar weakness (100% vs. 58%) and respiratory failure (46% vs. 7%) compared to seronegative patients. Moreover, greater involvement of the respiratory muscles was also reported in patients who tested positive for antimuscle specific kinase.

Electrodiagnostic EMG studies are nonspecific for myasthenia gravis, but a decrease of 10–15% in the amplitude of the action potential during slow repetitive nerve stimulation is seen in 77% of myasthenic patients. Single-fiber EMG is abnormal in 92% of the patients and is thought to be the most sensitive test, even in patients with a negative serum antibody against acetylcholine receptor or a normal repetitive nerve stimulation test.

Myasthenic crisis is defined as an exacerbation of myasthenia gravis leading to respiratory failure that necessitates the use of mechanical ventilation or the need for prolonged mechanical ventilation after surgery. Approximately 15–20% of myasthenia gravis patients will experience myasthenic crises, often within the first year of illness. Thymomas are associated with a more fulminate course of MG and are present in one third of patients who experienced myasthenic crises. Acute respiratory failure has been reported as the initial presentation of MG. The most common causes of myasthenic crises are respiratory infections (including aspiration) and surgery. Other precipitating factors include discontinuation or decreased dosage of anticholinergic or immune modulating medications, or the administration of new medications that precipitate MG. Commonly used medications such as corticosteroids, aminoglycosides and fluoroquinolones class of antibiotics, neuromuscular blocking agents, and neuropsychiatric drugs may precipitate myasthenic crises and should be avoided if possible. The initiation of corticosteroid therapy can paradoxically cause a transient increase in muscle weakness during the first or second week of therapy, especially in patients with severe bulbar symptoms and generalized myasthenia gravis. Cholinergic crisis due to excessive dosing of an anticholinesterase medication can mimic myasthenic crisis; this is thought to be due to a depolarization blockade at the neuromuscular junction. Other clinical signs of cholinergic crisis that are not present in myasthenic exacerbations include the presence of muscarinic symptoms such as miosis, hypersalivation, increased bronchial secretions, bradycardia, gastrointestinal symptoms (abdominal cramps, nausea, vomiting, and diarrhea), sweating, and muscle fasciculation. The Tensilon test has been used routinely in the past to differentiate myasthenic from cholinergic crises. However, this practice is currently not recommended because of the potential for respiratory arrest due to cholinergic weakness and increased secretions and mucus plugging, especially in patients with renal insufficiency. Moreover, it is now common practice to avoid dose escalation of cholinergic agents during myasthenic crises, to discontinue the use of cholinesterase inhibitors following intubations, and to reduce muscarinic complications.

Surgery, particularly thymectomy, is a recognized cause of myasthenic crises. In a series of 22 patients, the mean duration of mechanical ventilation was 8 days, with 6 patients (32%) requiring tracheostomy for prolonged mechanical ventilation. Postoperative monitoring is important because respiratory failure occurs within 24 h of surgery in more than 50% of patients. In a series of 14 of 122 patients who developed respiratory failures following trans-sternal thymectomy, independent predictors of postoperative myasthenic crises causing acute respiratory failure included preoperative bulbar symptoms, higher serum levels of acetylcholine receptor antibodies (>100 nmol/L), and intraoperative blood loss.

Serial measurements of FVC, maximum static respiratory pressures, and MVV are helpful in detecting significant respiratory muscle involvement and identifying patients at risk of acute respiratory failure. Both maximum static pressures and MVV correlated with clinical worsening of myasthenia gravis in a relatively stable outpatient setting. The dosing schedule of anticholinesterase medications will affect the measurement of these respiratory parameters. The maximum improvement in respiratory muscle strength occurs about 2 h after the drug is given and slowly declines until the next dose is given. Consequently, FVC, PImax, and PEep should be measured 30 min before the next dose of anticholinesterase agents. When FVC is below 15 mL/kg and the maximum static respiratory pressures are less than ±30 cm, assisted ventilation is likely required. No single respiratory parameter reliably predicts the need for mechanical ventilation. Other clinical signs of impending respiratory failure include upper airway obstruction due to vocal cord paralysis or the inability to handle oropharyngeal...
secretions due to severe bulbar involvement. Flow–volume loops may show variable extrathoracic airway obstruction with the characteristic inspiratory plateau. Bilateral basal atelectasis on chest radiograph signifies poor clearance of airway secretions due to a weak cough and is often accompanied by a rapid shallow breathing pattern. Hypercapnia is a late sign of respiratory muscle fatigue.

Treatment of myasthenia gravis includes anticholinesterase agents, high-dose corticosteroids, immunosuppressive medications such as azathioprine and mycophenolate, and cyclosporine as corticosteroid sparing agents. Anticholinesterase agents are the first line of treatment. Although anticholinesterase agents do not alter the natural course of the disease, most patients improve significantly with this treatment, but only a few patients regain normal function. Remission can be induced in up to 80% of patients with corticosteroids. However, initiation of corticosteroids therapy may cause temporary worsening of muscle weakness, usually on the 6th to 10th day of therapy. Thymectomy has also been shown to improve survival and clinical symptoms in patients with myasthenia gravis compared to patients who were treated medically, even in the absence of thymoma. Thymectomy can lead to clinical improvement and myasthenia gravis remission even in the absence of thymoma. Thymectomy is indicated in young patients (<55 years old) and in patients with thymoma because of the risk of malignant transformation. Because there are no randomized controlled studies documenting the benefit of thymectomy in myasthenia gravis, and given the presence of confounding variables such as age, gender, and severity of myasthenia gravis, the American Academy of Neurology recommends thymectomy in patients with nonthymomatous autoimmune myasthenia gravis only as an option to increase the probability of remission or improvement.

In patients with myasthenic crisis, plasmapheresis or intravenous immune globulin (IVIG) are effective short-term treatments and help to prepare the symptomatic myasthenia patient for surgery. Plasmapheresis is usually performed every other day utilizing exchanges of 2–3 L; a total of 5–6 exchanges is normative. Improvement in muscle strength is usually apparent in 2–3 days, but the improvement does not continue beyond several weeks unless immune suppressant agents are administered concurrently. Intravenous immune globulin given at 1.2–2 g/kg over 2–5 days has also been shown to result in a clinical response comparable to plasmapheresis. Plasmapheresis has a higher rate of cardiovascular and infectious complications compared to IVIG. Intravenous immune globulin infusion is an alternative treatment if plasmapheresis cannot be initiated because of vascular access problems or cannot be tolerated because of hemodynamic instability. Immunosuppressant medications are not appropriate therapy in myasthenic crises because a therapeutic response is often delayed for weeks to months. Corticosteroids have been used in patients who were refractory to plasmapheresis or IVIG; however, steroids may cause a transient worsening of muscle weakness. Corticosteroids and cholinesterase inhibitors are best started several days after a clinical response to plasmapheresis is observed, in order to avoid weakness due to corticosteroids and to avoid cholinergic crises.

Acute respiratory failure in patients with myasthenia gravis is usually treated with invasive mechanical ventilation. Noninvasive mechanical ventilation is an alternative ventilatory strategy in patients with severe myasthenia crises with early respiratory failure even in the presence of bulbar symptoms. In a retrospective study of 60 episodes of acute respiratory failure in 52 patients, bilevel positive airway pressure (BiPAP) and invasive mechanical ventilation were the initial method of ventilatory support in 24 and 36 episodes acute respiratory failure, respectively. In the BiPAP group, 14 (58%) were successfully treated with BiPAP alone and 10 eventually required invasive mechanical ventilation. The use of BiPAP avoids the need for airway intubation, decreases the duration of mechanical ventilation, and decreases both ICU and hospital length-of-stay. The only predictor of failure of using NPPV to initially treat respiratory failure in MG was a PaCO₂ of >45 mmHg. Thus, NPPV should be used early in acute respiratory failure before the onset of hypercapnia. In patients who required invasive ventilatory support, aggressive respiratory management including the use
of sighs, positive end expiratory pressure, frequent suctioning, chest physiotherapy, turning in bed, and the use of antibiotics decreased the prevalence of both atelectasis and bronchopneumonia.\textsuperscript{50} Weaning trials can be initiated once an improvement in respiratory status is documented. This includes a maximum inspiratory pressure (MIP) $<-20$ cmH\textsubscript{2}O, maximum expiratory pressure $>40$ cmH\textsubscript{2}O, and FVC $>10$ mL/kg.\textsuperscript{51} In a retrospective study of 46 episodes of acute respiratory failure due to myasthenia gravis, extubation failure defined as the need for reintubation, or tracheostomy and death while on the ventilator occurred in 44\% of cases. Risk factors associated with extubation failures include male sex, history of previous myasthenic crises, atelectasis, and $>10$ days of mechanical ventilation. The FVC (16 vs. 19 mL/kg, $p=0.32$), MIP (−46 vs. −56 cmH\textsubscript{2}O, $p=0.43$), and MEP (41 vs. 54, $p=0.14$) were lower in patients who failed extubation, but were not statistically different compared to patients who were successfully extubated. Those patients who had lower pH, lower FVC, the presence of atelectasis, and the need for BiPAP support had a higher risk for reintubation.\textsuperscript{52} These data suggest that other factors such as respiratory muscle fatigue, the presence bulbar weakness, and the inability to handle upper airway secretions are not measured by standard weaning parameters and should be considered before attempting extubation.

**Steroid Myopathy**

Myopathy is a well-recognized side effect of glucocorticoids therapy. Myopathy induced by glucocorticoids is largely due to their direct catabolic effects via gluconeogenesis and interference with the insulin-like growth factor-1 signaling, which leads to increased myocyte apoptosis. Steroid myopathy usually presents subacutely as proximal limb weakness, although high-dose corticosteroid therapy can induce clinically important weakness within 2 weeks of therapy. High-dose glucocorticoids given in conjunction with neuromuscular blocking agents may lead to critical illness myopathy as previously discussed (see Chap. 58). Myopathy can occur with any glucocorticosteroid preparation, but is unusual in patients treated with less than 10 mg/day of prednisone or its equivalent. Muscle enzymes are usually normal. EMG is either normal or reveals slight myopathic changes. In contrast to critical illness myopathy, a steroid-induced myopathy biopsy usually shows loss of type IIA muscle fibers with no evidence of inflammation or fiber necrosis. There is poor correlation between the total dose of steroids administered and the severity of muscle weakness. However, a gradual improvement in muscle strength follows discontinuation or reduction of administered corticosteroids.

**TREATMENT OF NEUROMUSCULAR DYSFUNCTION IN THE ICU**

The specific medical therapy for each of the neuromuscular disorders has been discussed previously. The proper care of these complicated patients often requires a multidisciplinary team of health care workers consisting of a pulmonary specialist, neurologist, respiratory therapist, physiatrist, physical therapist, and nutritionist. Once the acute life illness has resolved, some patients who have experienced difficulty weaning from the ventilator require prolonged care in a respiratory rehabilitation unit. Frequent family interaction with the health care team is beneficial to facilitate the transition of care from the ICU to a step-down unit.

**Mechanical Ventilation**

Ventilatory insufficiency leading to chronic respiratory failure is a common sequelae of progressive neuromuscular diseases. Acute respiratory failure is also common and is often precipitated by recurrent aspiration, lower respiratory tract infections, or other acute illnesses that place an additional burden on a limited ventilatory reserve. Pneumonia is strongly linked to the significant morbidity and mortality that patients with advanced chronic neuromuscular disease face. Once impending respiratory failure is recognized, mechanical ventilation...
should be used early to support spontaneous breathing until the acute precipitating event is identified and treated. The indications for mechanical ventilation are shown in Table 29-12. In patients who present with new onset of severe dyspnea, acute hypercapnia with respiratory acidosis, or moderate to severe hypoxemia associated with hemodynamic instability, endotracheal intubation and mechanical ventilation are necessary and preferred over noninvasive mechanical ventilation. In certain clinical situations, noninvasive positive pressure ventilation (NPPV) may be used to augment minute ventilation in patients who present with acute hypercapnic respiratory failure and who remain alert and cooperative with intact upper airway function and minimal airway secretions. All the patients described previously should be treated in the ICU, even those patients who tolerate the initial application of noninvasive positive pressure ventilation. Invasive and noninvasive mechanical ventilation are compared in Table 29-13.

Noninvasive ventilation has been shown to attenuate the decline in lung function and improve gas exchange, cognitive function, and survival in patients with neuromuscular disease. Noninvasive mechanical ventilation can be delivered as either NPPV or negative pressure ventilation (NV). The benefits and limitations of both forms of noninvasive mechanical ventilation are listed in Table 29-14.

Negative pressure ventilation, the iron lung in particular, was the first widely used method of mechanical ventilatory support in the management of respiratory failure due to neuromuscular diseases. During the poliomyelitis epidemics in the 1930s, negative pressure was highly effective in augmenting alveolar ventilation and decreasing the mortality due to poliomyelitis. The early success of NV in the treatment of acute respiratory failure due to poliomyelitis has since been repeated in patients with chronic respiratory failure from other forms of neuromuscular and chest wall diseases.

In recent years, NPPV has become the first choice of ventilatory support in patients with chronic respiratory failure due to a wide variety of neuromuscular diseases who have associated upper airway dysfunction. Because of the limitations of NV discussed earlier, it is now used only in patients unable to tolerate NPPV or is used during the daytime in combination with NPPV.

### Table 29-12

| Acute respiratory failure | Severe dyspnea |
|--------------------------|----------------|
|                          | Marked accessory muscle use |
|                          | Inability to handle secretions |
|                          | Unstable hemodynamic status |
|                          | Hypoxemia refractory to supplemental O₂ |
|                          | Acute respiratory acidosis |
| Chronic respiratory failure | Morning headache |
| Nocturnal hypoventilation | Lethargy |
|                          | Nightmares |
| Nocturnal oxygen | Enuresis |
| Desaturation | SaO₂ < 88% despite supplemental O₂ |
| Cor pulmonale | Due to hypoventilation with PaCO₂ > 45 mmHg, pH < 7.32 |

### Table 29-13

| Invasive ventilation (endotracheal intubation) |
|-----------------------------------------------|
| Copious secretions |
| Upper airway dysfunction |
| Inability to tolerate or failure of noninvasive ventilation |
| Impaired mental status |
| Unstable vital signs |
| Noninvasive ventilation |
| Awake, cooperative patient |
| Intact upper airway function |
| Minimal secretions |
| Stable vital signs |
with NPPV. In the ICU setting, we prefer NPPV over NV because of the ease of use and access to patients, its portability, and the maintenance of upper airway patency during sleep. Different types of masks may be used (nasal, oronasal, full face mask) for the application of NPPV depending on the patient’s comfort and preference, as well as to provide proper fit to minimize air leak. In patients with significant air leaks from mouth, chin straps may help close the mouth. Alternatively, an oronasal or full facemask often solves the problem of mouth leak in patients who are mouth breathers. Occasionally, facial ulcers or erythema may develop due to contact pressure from a particular mask interface. In this situation, using two different mask interfaces and rotating their use may promote healing of the facial ulcers and prevent recurrence, or allow a longer rest period between applications of NPPV that may improve patient tolerance.

Once a proper mask interface has been chosen, a wide variety of positive pressure ventilators may be used to deliver NPPV. In the intensive care setting, we prefer to use standard ICU ventilators because of the option of using either assist/control or pressure support mode or the combination of the two, depending on the clinical situation and patient preference. For example, synchronous intermittent mandatory ventilation (SIMV) combined with pressure support is useful in patients with nocturnal hypoventilation who have a decreased spontaneous respiratory rate as may occur during sleep. Some features that are available on standard ventilators that are useful in the acute clinical setting are the ability to monitor respiratory pattern and to supply variable amounts of enriched oxygen. In patients with acute or chronic respiratory failure who are otherwise hemodynamically stable, small pressure-limited, flow- or time-cycled portable ventilators (bilevel positive airway pressure) have been used with success. These devices are particularly useful in partial chronic ventilator support in patients with progressive neuromuscular dysfunction once the acute illness that requires ICU care has resolved.

The initial tidal volume or inspiratory setting of the ventilator should start at a low setting and ramp up gently, usually every 3–5 min based on patient tolerance, to achieve an increase in assisted tidal volume of 30–50% above baseline or a decrease of 5–10 mmHg in PaCO₂. The expiratory airway pressure on BiPAP is usually set at 4 cm to ensure continuous flow of gas during expiration, thereby flushing out the expired gas. If supplemental oxygen is required, oxygen tubing is connected to the ventilator tubing using a T-connector. The expiratory airway pressure may also be titrated up to increase FRC and improve gas exchange. The initial duration of ventilatory assistance depends on the severity of respiratory failure and patient tolerance. In an acute setting, ventilatory assistance of 20 h/day may be needed. In a chronic setting, we allow the patient to use NPPV during the daytime for a few hours, followed by nocturnal use of 6–8 h once they are accustomed to NPPV.

**SUMMARY**

The diagnosis of neuromuscular dysfunction should be considered in all patients with unexplained acute hypercapnic respiratory failure, acute-on-chronic hypercapnic respiratory failure, and in patients who fail to wean from ventilatory support after resolution of their acute
illness. In patients with rapidly worsening respiratory weakness, FVC less than 12–15 mL/kg indicates impending respiratory failure and the need to initiate ventilatory support. Other indications for ventilatory support include upper airway dysfunction, abnormal gas exchange, and hemodynamic instability. Noninvasive positive pressure ventilation may be used to provide partial ventilatory support in neuromuscular patients with hypercapnic respiratory failure who are awake, cooperative, hemodynamically stable, and with preserved upper airway function. The prognosis of patients with neuromuscular dysfunction who require ICU admission depends on the type and clinical stage of the neuromuscular disease, the nature of the precipitating illness, and the therapeutic response of the patient to medical interventions. In many cases of neuromuscular disorder, therapy is primarily supportive; avoidance of complications arising from the chronic illness is also crucial to patient recovery.

REVIEW QUESTIONS

1. Clinical predictors for the need of mechanical ventilation in patients with Guillain-Barre syndrome include:
   A. Inability to lift the head
   B. Rapid progression of clinical signs and symptoms
   C. Difficulty swallowing
   D. Presence of anti-GQ1b antibodies
   E. All the above

2. The following statements about the central respiratory drive are correct except:
   A. In normal individuals, there is an inverse linear relationship between oxyhemoglobin saturation and minute ventilation
   B. The increase in minute ventilation following an increase in PaCO₂ is much steeper compared to a similar unit decrease in oxygenation
   C. In patients with moderately advanced neuromuscular disease, central respiratory drive is uniformly depressed with the onset of chronic hypercapnic respiratory failure
   D. Assessment of central respiratory drive can be affected by profound respiratory muscle weakness
   E. P_100 is the best measure of the central respiratory drive

3. The common causes of muscle weakness in the ICU following life-threatening illness are these, except:
   A. Acute myopathy
   B. Critical illness polyneuropathy
   C. Protracted use of neuromuscular blocking agents
   D. Aminoglycoside-induced neuromuscular blockade

4. Optimal treatment strategies in myasthenic crises include all the following except:
   A. Immediate institution of plasmapheresis, or intravenous immunoglobulin infusion
   B. Temporary discontinuation of the anticholinergic agents for a few days until clinical improvement occurs following plasmapheresis to minimize the possibility of concomitant cholinergic crises
   C. Serial measurement of FVC and maximum inspiratory pressure to detect impending respiratory failure
   D. Rapid institution of NPPV when impending respiratory failure is imminent
   E. Immediate use of high-dose corticosteroid and dose escalation of anticholinergic agents

5. Risk factors in the development of critical illness polyneuropathy:
   A. Prolonged use of high-dose corticosteroids
   B. Hyperglycemia
   C. Prolonged mechanical ventilation of more than 7 days
   D. Vasopressors use of more than 3 days
   E. All the above

ANSWERS

1. The answer is E. Serial measurement of FVC is a useful test to detect impending acute respiratory failure. Early intubation should be strongly considered once the FVC is < 12 mL/kg. Other signs of impending respiratory failure include severe bulbar symptoms, inability to hold the head up, hypoxemia, and inability to handle oral secretions. The presence of anti-GQ1b and demyelinating form of GBS have also been reported as predictors of acute respiratory failure.

2. The answer is C. Except for some form of congenital myopathies, central respiratory is usually normal or slightly elevated in patients with neuromuscular disease. There is a linear increase in minute ventilation with every 1% decrease in oxyhemoglobin or 1 mmHg increase in PaCO₂. The linear relationship between hypercapnia and minute ventilation can be used to assess central respiratory drive. However, significant respiratory muscle weakness makes the
test inaccurate. P_{100}, by measuring the pressure generated very early during the inspiratory effort, is a more accurate test of the central respiratory drive since it is unaffected by the degree of respiratory muscle weakness.

3. The answer is D. Aminoglycosides may potentiate muscle weakness in susceptible patients with neuromuscular disorders. Acquired weakness in the ICU is most commonly the result of acute myopathy and critical illness polyneuropathy. Risk factors commonly associated with these conditions are sepsis, multisystem organ failure, shock, and prolonged use of neuromuscular blocking agents, especially in the presence of renal and hepatic failure.

4. The answer is E. Plasmapheresis is the treatment of choice in patients experiencing myasthenic crisis. IVIG can be used in lieu of plasmapheresis in patients who have hemodynamic instability or difficulty with central venous access. It is prudent to discontinue the anticholinergic agent during myasthenic crisis because of the possibility of concomitant cholinergic crisis. Corticosteroids can cause paradoxical weakness 5–7 days after starting corticosteroid treatment and should be withheld until clinical improvement is documented following plasmapheresis. NPPV decreases the need for invasive mechanical ventilation, and decrease the duration of ICU and hospitalization.

5. The answer is E. All have been identified as risk factors in ICU-acquired weakness. Approximately 70 to as high as 100% of patients with sepsis develop varying degrees of critical illness polyneuropathy. Prolonged use of mechanical ventilation; the need for vasopressor support for more than 3 days. Aggressive control of stress-induced hyperglycemia with intravenous insulin therapy has been done to decrease the incidence of critical illness polyneuropathy.

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**ADDITIONAL READING**

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