

Neuromuscular diseases and respiratory system

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- Neuromuscular diseases
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SUMMARY

The balance (gas exchange) between the atmosphere and the human body depends not only on the lungs but also in large part on the function of the “ventilator pump”, which consists of the respiratory control center which is located in the brain, the body rib cage, the diaphragm the intercostal, accessory and abdominal muscles. A wide variety of neuromuscular disorders (NMDs) can result in dysfunction of the ventilatory pump that can lead to respiratory failure, pneumonia and even death. Breathing disorders are recognized as the leading cause of mortality in neuromuscular disease and appropriate interventions can prevent complications and prolong life in individuals with neuromuscular disease affecting the respiratory system.¹

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INTRODUCTION

Neuromuscular disorders (NMDs) are disorders that affect the central nervous system such as the motor-nerve cells in the spinal cord, the peripheral nerves, the nerve-muscle (neuromuscular) junction and the muscles. This diverse group of disorders vary markedly in etiology, prognosis, rate of progression, therapy and of course, pattern of respiratory involvement.²

The ventilation impairment in MNDs depends on the specific disorder, such as disorders that affect one level (e.g isolated diaphragm paralysis) or different levels (e.g. multiple sclerosis) and the severity of impairment may be minimal and totally resolve with time and proper treatment (e.g. *Guillain-Barré syndrome*) or is characterized by relentless progression to eventual respiratory death (e.g. amyotrophic lateral sclerosis). Moreover, some NMDs concomitantly affect several structures (e.g. swallowing dysfunction in poliomyelitis, interstitial lung disease in polymyositis).

NMDs can be classified into diseases that involve the upper motoneuron, lower motoneuron or muscles themselves (Table 1).

The response of the respiratory system to moderate or severe NMDs is relatively stereotyped. The most common features are a reduced forced vital capacity (FVC), reduced respiratory muscle strength and malfunction of the neurons that control breathing. The breathing pattern is usually abnormal

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TABLE 1. Neuromuscular Diseases and motoneuron- muscles lesion.

Upper Motoneuron Lesions (pyramidal insufficiency)	Stroke Spinal Cord Injury Parkinson’s Disease Multiple Sclerosis (MS)
Lower Motoneuron Lesions	Poliomyelitis Amyotrophic Lateral Sclerosis (ALS)
Disorders of Peripheral Nerves	Diaphragm Paralysis Guillain–Barré syndrome (GBS) Critical Illness Polyneuropathy (CIP)
Disorders of the Neuromuscular Junction	Myasthenis Gravis Eaton –Lambert Syndrome Botulism
Inherited Myopathies	Duchenne’s Muscular Dystrophy (DMD) Myotonic Dystrophy Faciocapulohumeral Dystrophy (FSH) Limb- Girdle Dystrophy Acid Maltase Deficiency Mitochondrial Myopathy
Acquired Myopathies	Inflammatory Myopathies Systemic Lupus Erythematosus (SLE) Steroid Myopathy

and in early phases of NMDs, patients are either free of respiratory symptoms or have exertional dyspnea, not explained by obvious obstructive or restrictive lung disease. Physical examination may be unremarkable because generalized muscle weakness does not correlate with the degree of respiratory muscle involvement.³

Patients with respiratory muscle weakness have a low tidal volume (TV) and a high respiratory rate that persists in response to hypoxic or hypercapnic challenges. This rapid shallow breathing is not due to abnormalities in gas exchange (i.e. hypoxemia or hypercapnia) but is more likely to be due to severe muscle weakness and/or impaired afferent and efferent connections of the motoneurons by the underlying neuromuscular disease (Table 3).

**UPPER MOTONEURON LESIONS/
PYRAMIDAL INSUFFICIENCY**

Stroke

Hemispheric ischemic strokes reduce chest wall and diaphragm movement on the side contralateral to the cerebral insult. Bilateral hemispheric strokes are usually associated with Cheyne- Stokes respiration, which is

TABLE 2. NMDs and clinical assessment

Assesment	Clinical History	Physical Exam	Pfts	Sleep Testing	Thorasic Imaging
Bulbar Weakness	Aspiration	Change in appearance	Difficulty with testing due to poor mouth seal	In any patient with nocturnal symptoms or progressive decline in FVC	Low lung volumes Pneumonia Pulmonary embolism
	Drooling				
	Voice change	Drooling			
	Post prandial cough				
Diaphragm/ inspiratory muscles	Orthopnea	Sleepy	Restrictive pattern	Decrease Sat <90% for >5 min	
	Dyspnea on bending	Increased RR	↓TLC, ↑RV	Hypoventilation and/or obstructive sleep apnea	
	Sleepiness	Shallow breathing	↓PIP		
	Morning headaches	Orthopnea	↓SNIP		
	Decreased stamina speaking	Accessory muscle use	FVC (supine): drop >20%-30% DLCO: normal or ↓		
Expiratory muscles	Recurrent infections	Decrease in cough volume	Sniff test :abnormal		
	Cough		MIP ≤30ccH ₂ O MEP <40 ccH ₂ O Peak cough flow <270 L/min ABGs: pCO ₂ >45mmHg		

TLC: Total Lung Capacity, FVC: Forced Vital Capacity, RV: Residual Volume, DLCO: diffusing capacity for carbon monoxide, MEP: maximal expiratory pressure, MIP: maximal inspiratory pressure, PIP: Peak inspiratory pressure, SNIP: sniff nasal inspiratory pressure.

TABLE 3. Indications of potential pulmonary involvement⁹²**SpO₂**SpO₂ <94%SpO₂ <92% for those with lung diseaseSpO₂ >94% (or >92% for those with lung disease) but with sleep related respiratory symptoms: refer for sleep studies**ABGs**PaCO₂ >45 mmHg: refer to a specialised servicePaCO₂ <45 mmHg, with symptoms (orthopnoea): refer to a specialised service and/or for sleep studies**VC or FVC**

VC or FVC <50% predicted

VC or FVC <80% predicted with symptoms (orthopnoea) consider: (a) VC standing and lying & (b) sleep study

SNIP and/or MIPSNIP or MIP <40 cmH₂OSNIP or MIP <65 cmH₂O for males or 55 cmH₂O for females, plus any symptoms (particularly orthopnoea)Decline >10 cmH₂O over a 3-month period

progressive hyperventilation alternating with hypoventilation and ending in apnea. This breathing pattern may result from increased responsiveness to carbon dioxide as a result of interruption of normal cortical inhibition.

In descending order of frequency, the most fatal complications of ischemic stroke are bacterial pneumonia, pulmonary embolism, myocardial infarction, and sepsis without pneumonia (often in the setting of a urinary tract infection).⁴

Stroke-associated pneumonia (SAP) has been implicated in the morbidity and mortality after acute ischemic stroke. SAP is described as early when it happens in the first 72 h of admission to the hospital. Another classification in use divides SAP into acute (when pneumonia develops within a month of stroke) and chronic (when it occurs later than a month).⁵

SAP is thought to be secondary to aspiration. Aspiration and its related risk factors such as impaired level of consciousness and dysphagia have been found to be important risk factors for SAP.⁶ Many stroke patients have impaired swallowing mechanisms leading to aspiration of oral content during sleep, which theoretically may be related to abnormal dopamine transmission.^{5,7}

Spinal Cord Injury

Spinal cord injury is most commonly due to traumatic injury caused by motor vehicle accidents, falls, sports ac-

cidents and gunshot wounds. Cervical spinal cord injury (SCI) severely compromises respiratory function due to paralysis and impairment of the respiratory muscles. Respiratory complications such as atelectasis, pneumonia and respiratory failure are common,^{8,9} and a primary cause of both short and long-term morbidity and mortality.¹⁰

After acute SCI, a number of pathophysiologic changes can affect the respiratory system and predispose to respiratory complications, such as 1) cough inefficiency due to expiratory muscle weakness, 2) ciliary dysfunction, 3) mucous hypersecretion possibly due to impairment of the peripheral autonomous nervous system, 4) glottis dysfunction or gastric hypomotility increasing the risk of aspiration and 5) loss of consciousness at the time of the injury, increasing the risk of aspiration.^{11,12}

The degree of respiratory impairment depends on the level and extent of the spinal cord injury.¹³

Initially the patients are threatened by acute loss of motor function of the respiratory muscles and the development of neurogenic pulmonary edema, whereas changes in lung function, pulmonary infections and airway problems are the main reasons for life threatening respiratory failure. The FEV₁ and PEF are much lower in smokers as well.¹⁴

Early surgical stabilization, careful weaning from mechanical ventilation, meticulous search and treatment of infections, aggressive posturing and mobilization and support of impaired mechanical functions by physiotherapy, muscle training, noninvasive respiratory support and in some cases electrophrenic pacing increase survival and independency of quadriplegic patients.¹⁵

Various types of respiratory muscle training (RMT) (i.e. respiratory muscle strength and endurance) have been described in the literature, in order to improve respiratory function for people with cervical SCI. RMT is effective for increasing respiratory muscle strength and perhaps also lung volumes for people with cervical SCI.^{16,17}

Parkinson's Disease

Respiratory abnormalities are common in Parkinson's disease, with pneumonia being the most common cause of death. Parkinson's disease results in disordered coordination and activation of upper airway and chest wall muscles that may result in functional glottis obstruction and/or failed coordination of repetitive respiratory tasks. The substantial problem with Parkinson's disease is glottis muscle dysfunction. An abnormal flow-volume loop contour showing regular or irregular flow oscillations commonly occurs. Physiological evidence of upper-airway

obstruction may be present. In addition to the presence of flow oscillations, a rounding off of the peak of the midexpiratory flow-volume curve and a lowered peak expiratory flow rate have been observed in Parkinson's patients. All these abnormalities are favorably treated with antiparkinson medications.¹⁸

Levodopa is considered the gold standard therapy for Parkinson's disease (PD). Some studies suggest that levodopa therapy improved FVC and PEF, whereas no changes are observed in FEV(1) and FEV(1)/FVC. These findings may provide some indirect evidence regarding the efficacy of levodopa in restrictive parameters of pulmonary function.^{19,20}

Multiple Sclerosis

MS is a demyelinating disorder of the CNS, characterized clinically by "relapsing remitting" pattern, in which there are clearly defined symptomatic attacks lasting 24 hours or more, followed by complete or almost complete improvement. Because MS can cause focal lesions anywhere in the central nervous system, different patterns of respiratory impairment can occur. Involvement of the respiratory center in the medulla can cause failure of automatic breathing (Ondine's curse), apneustic or neurogenic pulmonary edema. The three most common respiratory manifestations of MS are respiratory muscle weakness, bulbar dysfunction and abnormalities on respiratory control.

When respiratory motor pathways are involved, respiratory muscle impairment and subsequent acute or chronic ventilatory failure may ensue. As in other neuromuscular diseases, respiratory muscle weakness, abnormal control of breathing, or increased respiratory system elastance with increased work of breathing may be involved in the respiratory disturbances in MS.²¹

In patients with clinically stable, moderately severe multiple sclerosis, the respiratory muscle function is abnormal.²² Diaphragmatic paralysis resulting in respiratory insufficiency has also been reported. Even with severe disability and impaired respiratory muscle strength, patient with MS seldom complain of dyspnea. This paucity of respiratory complaints may be due to restricted motor activities and greater expiratory than inspiratory muscle dysfunction. Clinical signs that may be helpful is predicting respiratory muscle impairment are weak cough and inability to clear secretion, limited to count on a single exhalation and upper extremity involvement, Advanced MS is frequently complicated by aspiration, atelectasis and

pneumonia. Acute respiratory failure rarely occurs in this disease, but it can occur in case of severe demyelination of the central spinal cord.²³

Trends for improvement following respiratory muscle training are observed for expiratory muscle strength, vital capacity and residual volume.³ Breathing exercises with positive expiratory pressure are often recommended to patients with advanced neurological deficits and may be beneficial in patients with mild to moderate stages of MS.^{24,25}

LOWER MOTONEURON LESIONS

Poliomyelitis

Paralytic poliomyelitis, an acute disease caused by poliovirus, has been part of human history for thousands of years. In the mid-twentieth century, after the introduction of an effective vaccination program, the number of new cases dramatically dropped. Respiratory muscle paralysis is the most devastating of the clinical manifestations of poliomyelitis infection and is preceded by a period of fever and mild illness. Respiratory motor nuclei may be directly involved, resulting in diaphragmatic or other respiratory muscle dysfunction. Moreover, the central respiratory centers can be directly affected, resulting in irregular respirations. In contrast to Guillain-Barré syndrome, sensation is intact. Many patients require aggressive ventilator and hemodynamic support during the acute phases of their illness.²⁶

Some patients with a history of poliomyelitis report late-onset neuromuscular symptoms and a decline in functional capacity.²⁷ These late symptoms are referred to as post-poliomyelitis syndrome (PPS). The syndrome is characterized by new and increased muscle weakness, fatigue, muscle pain, joint pain, muscle cramps, cold intolerance, and lung problems.^{28,29}

In patients with poliomyelitis, respiratory failure requiring ventilatory support may occur during the acute illness. Some patients continue to require long-term nocturnal ventilatory support; others are weaned but subsequently require support because of a late deterioration in ventilatory function.³⁰

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive neurodegenerative disease of the motor neurons in the cerebral cortex and spinal cord, which results in weakness and atrophy of voluntary skeletal muscles.³¹

The result is a combination of upper and lower motoneuron dysfunction, manifested by spasticity and hyperreflexia muscle wasting, weakness and fasciculations. The usual clinical presentation is progressive weakness of the distal extremities, although severe respiratory muscle weakness, particularly intercostal muscle and diaphragm weakness presents with respiratory insufficiency as the initial manifestation. Progression of respiratory impairment as well as reduction in FVC and MMV are much faster in ALS than other chronic neuromuscular disorders. In contrast to patients with other neurological disorders, slightly elevated transpulmonary pressure at FRC and RV is usually increased and continues to rise as the disease progresses with maintenance of normal TLC. These changes are thought to be due to earlier involvement of the abdominal musculature, with preservation of intercostals and diaphragm function.

The shape of the flow-volume curve may also pinpoint the subgroup of ALS patients with greater weakness of the expiratory muscles. In patient with severe expiratory muscle weakness, the flow-volume curve near RV shows a sharp drop in flow such the maximum expiratory curve has a concave appearance. Additionally to respiratory dysfunction, sleep-disordered breathing is common and noninvasive nocturnal ventilation can be highly effective.³²

The use of respiratory muscle testing has been used to help determine the prognosis and help clinicians decide when to initiate ventilatory assistance. Recently, the sniff nasal inspiratory pressure (SNIP) was used to predict survival in ALS. A sniff is a short voluntary inspiratory maneuver, which has been shown to correlate with invasive non volitional test of diaphragm strength.³³

Difficulty in swallowing food or even saliva predisposes ALS patient to markedly increased risk of pulmonary aspiration. The advanced age at diagnosis and airway mucus accumulation represent factors of poor prognosis for ALS patients treated with NIV while airway intubation may be required because of bulbar dysfunction further impairing cough and the inability to clear secretions.^{33,34,37}

Currently, guidelines from the American Academy of Neurology recommend treatment with noninvasive mechanical ventilation once the FVC is below 50 per cent of predicted. Also, ventilation with bi-level positive airway pressure has been shown to increase both survival and quality of life in patient with ALS, while those with orthopnea seemed to derive the most benefit.^{35,36} However, concerns remain that progressive disability may negate these benefits.³⁸

DISORDERS OF PERIPHERAL NERVES

Diaphragm Paralysis

Unilateral or bilateral diaphragm paralysis following phrenic nerve injury can result from cardiac surgery, trauma, mediastinal tumors, infections of the pleural space and forceful manipulation of the neck. Diaphragm paralysis may also be seen with a variety of motoneuron diseases, myelopathies, neuropathies and myopathies, as well COPD and other diseases that cause lung hyperinflation.

Unilateral diaphragm paralysis is more common than the bilateral one. The list of potential causes is similar. The most frequent causes of unilateral paralysis include phrenic nerve injury related to cardiac or thoracic surgery, herpes zoster, cervical spinal disease, or invasive or compressive tumors.³⁹ In unilateral diaphragm paralysis, patients may be asymptomatic at rest but have dyspnea with exertion.⁴⁰ Orthopnea may be present but is not as common or severe as in bilateral paralysis.

The diagnosis is often suggested by an elevated hemidiaphragm on chest x-ray and confirmed with a fluoroscopic sniff test. In this test, an upward or "paradoxical" movement of the paralyzed hemidiaphragm is seen during a vigorous sniff maneuver performed by the patient.⁴¹

Bilateral diaphragm paralysis is characterized by severe restrictive ventilatory impairment, with impaired pulmonary function and significant drops of VC in the supine position of up to 50%.⁴²

TLC is also markedly decreased, as well as FRC and static pulmonary compliance. In most patients with nontraumatic bilateral diaphragm paralysis, the most important clinical feature is orthopnea out of proportion to the severity of the underlying cardiopulmonary disease. Sleep-disordered breathing with hypoventilation and hypoxemia is common as well and can be treated with NIMV.^{43,44}

Interestingly, bilateral diaphragmatic paralysis can be difficult to diagnose. For one thing, there is no normal hemidiaphragm to use for comparison with an abnormal one. Therefore, chest radiography and fluoroscopic sniff testing can yield false negative results. Two-dimensional echocardiography of the movement of the diaphragm dome shares the same limitations as fluoroscopy.⁴⁵ Phrenic nerve conduction studies can be useful in diagnosing a neuropathic cause of diaphragmatic paralysis but can have technical limitations.⁴⁶ Diaphragm electromyography measurements may be useful, but technical issues such as "cross-talk" from adjacent muscles, electrode placement,

or variable muscle-to-electrode distances due to subcutaneous fat limit its utility. The "gold standard" diagnostic test is measuring transdiaphragmatic pressure using a thin balloon-tipped polyethylene catheter placed in the esophagus and stomach and showing a lack of ability to generate a transdiaphragmatic pressure.⁴⁷

Electromyography of the diaphragm is technically difficult and its results can therefore be hard to interpret or rely upon. It can potentially help differentiate between a myopathy and neuropathy, if one of these is strongly believed to be the cause of diaphragmatic dysfunction. Finally, dynamic MRI of the diaphragm has been recently described in the literature as a tool allowing more detailed study of diaphragmatic dysfunction.^{48,49}

Guillain-Barré syndrome (GBS)

GBS precipitates respiratory failure more often than any other peripheral neuropathy. It is an acute idiopathic polyneuritis and usually presents as paresthesia and ascending paralysis of the lower extremities with absent deep tendon reflexes in a symmetrical distribution. The distribution of muscle weakness between respiratory and nonrespiratory muscles is not uniform in GBS and peripheral muscle strength does not correlate with the presence or absence of respiratory muscle weakness. However, ventilator failure collates with diaphragmatic weakness.

GBS affects the respiratory system by causing (1) weakness of the upper airway muscles, (2) weakness of the inspiratory and expiratory muscles, and (3) secondary complications such as pneumonia or pulmonary embolism.⁵⁰ Approximately 25% to 50% of patients develop respiratory insufficiency severe enough to necessitate intubation and mechanical ventilation.^{51,52} Despite medical treatment, GBS often remains a severe disease; 3-10% of patients die and 20% are still unable to walk after 6 months.

With rapidly progressive disease, the intensive care unit (ICU) is considered the best setting for monitoring.⁵³ Absolute indications for intubation include impaired consciousness, respiratory or cardiac arrest, shock, arrhythmias, blood-gas alterations, or bulbar dysfunction with confirmed aspiration. Noninvasive ventilation is generally not an option for these individuals because they are at a high risk for aspiration because of bulbar muscle involvement.⁵⁴

Critical Illness Polyneuropathy (CIP)

Critical illness polyneuropathy (CIP) and myopathy

(CIM) are major complications of severe critical illness and its management. CIP/CIM prolongs weaning from mechanical ventilation and physical rehabilitation since both limb and respiratory muscles can be affected.⁵⁵ The major risk factors for critical illness polyneuropathy include sepsis and systemic inflammatory response syndrome (SIRS),⁵⁶ treatment with steroids⁵⁷ or neuromuscular blocking agents,⁵⁸ and hyperglycemia.⁵⁹ Other factors that are thought to contribute to this disorder include total parenteral nutrition, aminoglycoside use, catecholamines, hyperosmolality, female gender, longer duration of multiorgan failure, greater illness severity, and renal failure.⁶⁰

The patients typically exhibit varying degree of musculoskeletal weakness, which range from mild weakness to near total paralysis with diminished deep tendon reflexes. Unfortunately, physical examination is unreliable as the sole means of diagnosis and electromyography with nerve conduction studies (EMG/NCS) are required to confirm the diagnosis.

Patient who develop CIP tend to require a longer period of mechanical ventilation and longer hospital stays compared with those without CIP. Additionally, the weakness associated with CIP results in an extended rehabilitation period, and there is evidence of persistent neuropathy on EMG/NCS as long as 5 years after discharge from the intensive care unit. Because no specific therapy for CIP exists, treatment is purely supportive and includes aggressive rehabilitation, nutrition support and treatment of any medical complication.

Compared with demyelinating diseases such as Guillain-Barré syndrome, critical illness polyneuropathy has normal nerve conduction velocity; compared with rhabdomyolysis, critical illness polyneuropathy will have a normal creatine phosphokinase, lack of muscle tenderness, and minimal electromyographic changes; and compared with cachectic myopathy, critical illness polyneuropathy is not usually associated with severe malnutrition.⁶¹

DISORDER OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Myasthenia gravis is the most common disease affecting neuromuscular transmission and nowadays the term 'myasthenia gravis' includes heterogeneous autoimmune diseases, with a postsynaptic defect of neuromuscular transmission as the common feature.^{62,63}

It causes weakness of several muscle groups including

the respiratory muscles, which are particularly susceptible to fatigue during the severe, potentially life-threatening, exacerbations, requiring intubation and mechanical ventilation, known as *myasthenic crisis*.⁶⁴⁻⁶⁶

Acute respiratory failure and recurrent pneumonias due to aspiration from bulbar involvement and impaired cough are the most common complications of myasthenic crisis.

BiPAP can be tried first in selected patients with acute respiratory failure especially due to myasthenic crisis and possibly other causes, while awaiting improvement from other specific therapies. However, it should be stressed, that there is a need for closer cardiac monitoring, as patients with myasthenic crisis are prone for cardiac arrhythmias. Also, repeated clinical assessment and arterial blood gas measurements for the first 6–8 hours are generally required to judge the efficacy of NIV and the need for invasive ventilation.⁶⁷

Eaton –Lambert Syndrome

LEMS is a myasthenic syndrome associated with small cell lung cancer (3% of cases) that can affect the respiratory muscles in a fashion similar to that of myasthenia gravis.⁶⁸ In patients with LEMS, SCLC may also be occult and should be sought for up to 5 years after the diagnosis of LEMS. Although respiratory involvement is often a late finding, true respiratory failure can be a manifestation of LEMS,⁶⁹ and this disorder should be considered in individuals with unexplained neuromuscular weakness.

LEMS shares a similar pathophysiologic mechanism with myasthenia gravis, but the clinical presentation is different and is characterized by:

- (1) an increase in the compound muscle action potential with repetitive nerve stimulation, a feature not seen in myasthenia,
- (2) more frequent presence of proximal leg weakness, which is worse in the morning,
- (3) greater autonomic dysfunction, and
- (4) frequent association with malignancy.⁷⁰ Respiratory muscle weakness is often detected on pulmonary function tests but respiratory failure is infrequent.⁷¹

Botulism

Botulism is a neuroparalytic syndrome that is caused by a toxin produced by the gram-positive bacterium *Clostridium botulinum* (A-F toxins)⁷². The botulinum toxin is one of the most potent toxins known. The clinical syndrome is one of progressive paralysis with early cranial nerve involvement causing blurred vision, dysphagia, dysarthria,

and facial weakness. Descending muscle weakness is the usual course and involvement of the upper airway, diaphragm, and intercostal muscles often leads to the requirement for intubation and mechanical ventilation.⁷³

Spirometry usually reveals a restrictive ventilatory defect and recovery of muscle strength from the injury requires regrowth of new synapses, a process that can take 6 months, often requiring prolonged mechanical ventilation. Early diagnosis and management rely on history and physical examination. Treatment requires intensive care that includes mechanical ventilation, when necessary, and administration of antitoxin. Delay in treatment may allow progression of paralysis, protracted hospitalization and deaths of long-term mechanical ventilation and intensive care unit care. The clinicians must take this disease into consideration of a possible outbreak.^{74,75}

INHERITED MYOPATHIES

Duchenne muscular dystrophies

DMD is a progressive myopathic disorders caused by mutations of the dystrophin gene on chromosome Xp21.⁷⁶

Symptoms usually present in the early childhood.⁷⁷ Gait disturbances and delayed motor development are common manifestation with proximal weakness resulting in an exaggerated lumbar lordosis. Kyphoscoliosis commonly develops as a result of severe muscle weakness and further contributes to a restrictive ventilatory deficit. Pulmonary symptoms are often minimal early on, despite significant weakness of the respiratory muscles. Maximum inspiratory pressure is reduced at all lung volumes in patients with DMD and declines time. FVC increased with growth during the first decade and may mask early respiratory muscle dysfunction before it plateaus and progressively decreases about 5 to 6 percent after 12 years of age.

Despite the severe and progressive muscle weakness, hypercapnia is uncommon in patients with DMD in the absence of pulmonary infections. This absence of hypercapnia is believed to be due to relative preservation of diaphragm function until very late in the illness. Once hypercapnia occurs, however, the course is rapidly progressive and the means survival is approximately 10 months. Management of a patient with DMD is mainly supportive.

Maintenance of cough and adequate airway clearance is extremely important in attempting to prevent atelectasis and pneumonia in this patient population.

Respiratory tract infections are a serious complication in DMD patients and must be treated aggressively with physiotherapy, postural drainage, assisted cough techniques and appropriate antibiotics. All patients, regardless of cough status should receive vaccination against pneumococcal pneumonia and influenza. In some patients, assisted ventilation is required once respiratory insufficiency or symptoms of sleep-related breathing disorders are present.^{78,79}

Myotonic Dystrophy (MD)

MD is the most common form of hereditary muscular dystrophy in adults. Symptoms such as muscle weakness are common and can be severe, despite mild limb muscle weakness. Myotonia of the respiratory muscles contributes to an increased work of breathing by increasing inspiratory impedance. Studies have suggested that the presence of a chaotic breathing pattern may explain the higher prevalence of chronic hypercapnia in patient with myotonic dystrophy than in patient with other forms of muscular dystrophy.

Patient with myotonic dystrophy are particularly susceptible to development to respiratory failure with general anesthesia and sedatives. Postoperative respiratory monitoring is essential if surgery or the use of these agents is required. Pharyngeal and laryngeal dysfunction increases the risk of aspiration and Sleep-related breathing disturbances are common and may include both central and obstructive forms of sleep apnea.⁸⁰

In patients with MD, chronic pCO₂ retention was associated with the presence of impaired central control of breathing⁸¹ and nocturnal positive-pressure ventilation should be tried when hypercapnia and hypoxemia are present.

Facioscapulohumeral Dystrophy (FSH)

FSH is an autosomal dominant dystrophy that primarily affects muscles of the face and proximal portion of the upper extremities. Respiratory muscle weakness is relatively unknown in FSH, but it is not uncommon.⁸² In patient with FSH, the FVC is significantly reduced, although facial weakness complicates spirometric assessment.

Limb- Girdle Dystrophy

Limb- Girdle Dystrophy is a heterogeneous group of autosomal dominant recessive disorders. The disease usually presents in the 2nd or 3rd decade of life and several case reports have documented the development of chronic

hypercapnia in patients with limb-girdle dystrophy who have severe diaphragm weakness or bilateral diaphragm paralysis as the basis for hypercapnia. However, not all patients develop hypercapnia, most have moderate respiratory muscle weakness with normal gas exchange.⁸³

Mitochondrial Myopathy

Mitochondrial Myopathy represents a heterogeneous group of disorders that affect mitochondrial function and may present as complex multisystem disorders with brain and striated skeletal muscle being the predominant organs affected: (a) Kearns – Sayre syndrome (b) myoclonic epilepsy, “ragged red fibers” and mitochondrial myopathy © encephalopathy, lactic acidosis and stroke-like episode.

The clinical manifestations may be broad and include myalgia and exercise intolerance, proximal muscle weakness and external ophthalmoplegia. All three disorders are characterized by hypoventilation and depressed responses to hypoxia and hypercapnia and in some cases, unexplained respiratory failure.⁸⁴

ACQUIRED MYOPATHIES

Acquired Myopathies include inflammatory polymyopathies (polymyositis and dermatomyositis), systemic lupus erythematosis, endocrine myopathies (hyper- hypothyroidism), hyperadrenocorticism, electrolyte disturbances, rhabdomyolysis and the use of high dose exogenous corticosteroids.

Pulmonary complications are the major cause of morbidity and mortality in **polymyositis and dermatomyositis**. These include interstitial pneumonitis, pulmonary vasculitis, and recurrent aspiration from oropharyngeal dysfunction and rarely hypoventilatory failure from respiratory muscle weakness.

Symptoms related to respiratory muscle weakness usually are not the presenting complaints. However, respiratory muscle weakness can occur in 5% to 10% of the patients with dermatomyositis and polymyositis⁸⁵ and may be found in as many as 75% of individuals if respiratory muscle function is carefully evaluated.⁸⁶ Interstitial lung disease may occur in up to 70% of patients with dermatomyositis or polymyositis.⁸⁷ Individuals diagnosed with dermatomyositis or polymyositis should be evaluated for the presence of restrictive pulmonary disease, which may be due to respiratory muscle weakness as well as underlying interstitial lung disease.

In patients with **systemic lupus erythematosis**, dia-

phragm dysfunction and respiratory muscle weakness with small lung volumes occur without apparent involvement of the peripheral skeletal muscle. This syndrome has been called "the shrinking lung syndrome".⁸⁸ Decreased lung volumes do not appear to be due to parenchymal lung disease or phrenic neuropathy but, rather to a myopathic process affecting diaphragm strength. It is estimated that approximately 25 percent of SLE patients have diaphragm weakness, even in the absence of a generalized myopathy.

Finally, although **steroid-induced myopathy** was first described almost 30 years ago, the development of severe respiratory muscle weakness and prolonged respiratory failure following the use of high dose steroids, usually in asthmatic patients in ICU, has received renewed interest.^{89,90} Some patients require months of mechanical

ventilation before eventual recovery. The serum CPK and EMG data show nonspecific changes. Overall, it is difficult to incriminate specific neuromuscular blocking agents or steroids as the only factors responsible for myopathic changes because an underlying severe illness, under nutrition, multiple medication and disuse atrophy are usually concurrent.⁹⁰

NONINVASIVE VENTILATION IN NEUROMUSCULAR PATIENTS

NIV can be used to deliver bilevel (Bipap) or continuous positive airway pressure (CIPAP). CiPAP can help to overcome upper airway resistance and keep alveoli open but this mode provides little support to the respiratory

TABLE 4.

Indications and relative contraindications for the use of NIV in patients with NMDs.

Indications	Relative Contraindications
Myasthenic exacerbation/crisis	Guillain –Barre syndrome
Neuromuscular disorders with exacerbated COPD or CHF	Spinal cord injury in acute phase
Neuromuscular failure with persistent weakness after extubation	Acute brain disease and coma
Motor neuron disease (ALS etc)	Severe agitation requiring sedation
Muscular dystrophies	Excessive respiratory secretions
	Severe acute systemic complication (shock, myocardial ischemia, unstable arrhythmias)

Indication for Invasive Ventilation in Patient with NMDs

Acute Respiratory failure

Severe dyspnea
Excessive accessory muscle use
Copious Secretions
Instable hemodynamic state
Severe hypoxemia refractory to supplemental oxygen
Acute ABGs disturbances (increased pCO₂ with pH >2.25)

Chronic respiratory failure

Nocturnal Hypoventilation
Increased work of breathing
Cor pulmonale or pulmonary hypertension

Nocturnal desaturation (Sat <88%) despite supplemental O₂ therapy

Indications for Tracheostomy in patients with NMDs

- Constant and fixed large airway obstruction (prolonged translaryngeal intubation)
- Intermittent and dynamic large airway obstruction (eg multisystem atrophy)
- Secretion management in patients choking on excessive oropharyngeal secretions in bulbar motor neurone disease or severe neuromuscular disease
- Weaning from prolonged invasive mechanical ventilation
- Management of patient with NIV who either cannot be ventilated effectively or are spending most of the day on ventilation

COPD: chronic obstructive disease; CHF: congestive heart failure; ALS: amyotrophic lateral sclerosis

muscles and it is not ideal in neuromuscular patients. For this reason, the use of BiPAP is the best strategy because Inspiratory positive airway pressure (IPAP), expiratory positive pressure (EPAP) and flow of oxygen, should be tailored to the individual situation.⁹¹

Additionally, the patients with NMDs are likely to require ventilatory support in the long term but the issue about whether to perform a tracheostomy is a big problem, as once performed it may be difficult to decannulate the patient and provide support with NIV. The ability of clinicians to predict which patients will require prolonged ventilatory support is limited but the ability to clear secretions is the key if the patients can be decannulated.

Finally, ventilation via tracheostomy is an alternative for NMDs patients but the decision on tracheostomy depends more on professional and patient views and wishes than on strictly medical criteria, however decannulation usually is difficult if cough flows are <160 lt/min, even with the addition of cough insufflations-exsufflation device⁹² (Table 4).

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