

A Pulmonologist's Approach to Neuromuscular Disease

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Educational Objectives:

1. Recognize the potential pulmonary complications of progressive neuromuscular disorders including:
 - i) Ventilatory dysfunction
 - ii) Ineffective cough
 - iii) Upper airway dysfunction and aspiration
 - iv) Sleep disordered breathing
2. Develop a systematic approach to the evaluation of patients with neuromuscular disease
3. Be familiar with interventions in respiratory care that have significantly improved outlook, including survival and quality of life in patients with neuromuscular disease

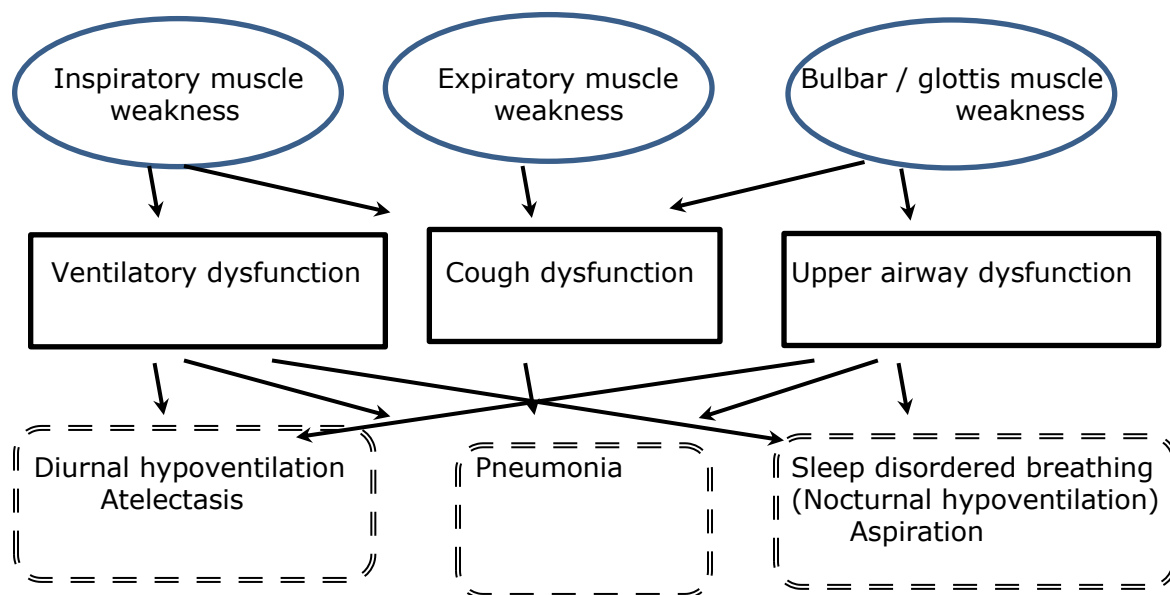
Scenario:

Michael is a 21-year-old male with Duchenne Muscular Dystrophy (DMD) who presents to your clinic to transition care from the Children's Hospital. He brings no medical records with him. He has no complaints stating he was just told he would need to follow up with a pulmonologist. He denies any dyspnea, chest pain or cough. He brings with him a list of his medications which include enalapril, omeprazole, montelukast, fluticasone, glycopyrrolate, and Vitamin D. On examination, his vitals are BP 116/68, HR 90, RR 22, SpO₂ 98% RA. He is seated comfortably in a motorized wheelchair. He has limited head flexion, JVP flat with regular heart sounds. There is a midline scar on his back with asymmetrical breath sounds but no additional sounds. He has limited movement of his fingers only. There is no peripheral edema.

Question 1: What are the potential pulmonary complications of neuromuscular disorders and what, if any, testing should you do?

Pulmonary complications are the leading cause of death in progressive neuromuscular disorders. A systematic approach for evaluation is helpful to provide appropriate clinical care.

One approach is to think about the functions of the respiratory system using an anatomical organization:



Adapted from Benditt JO, Boitano LJ. Pulmonary Issues in Patients with Chronic Neuromuscular Disease. *Am J Respir Crit Care Med.* 2013; 187(10): 1046-1055, Figure 1

In-depth knowledge about the wide range of neuromuscular diseases is beyond the scope of most pulmonologists. However, a basic understanding of the pattern of muscle involvement, rate of progression, the presence of co-existing restrictive chest wall disease, and the presence of cardiac involvement regarding your patient's specific neuromuscular condition is helpful.

Regular **evaluation** for pulmonary complications is recommended in patients with neuromuscular disease. A systematic approach is suggested and evidence for dysfunction in each of the following domains should be sought at each clinic visit through clinical history, physical examination and directed diagnostic testing.

i) **Ventilatory function**

- Signs and symptoms of decreased ventilatory function include: Dyspnea, morning headaches, tachypnea, hypoxemia, use of accessory muscles, paradoxical chest-abdominal breathing
- Diagnostic testing:
 - Sleep evaluation – See below. In the absence of acute illness, the first signs of respiratory insufficiency occur during sleep. Nocturnal hypoventilation precedes diurnal hypoventilation. Daytime tests of lung function do not reliably identify patients with sleep disordered breathing in the absence of diurnal hypercapnia, so polysomnography can be considered to help identify sleep disordered breathing and nocturnal hypoventilation.
 - Pulmonary function testing –
 - Vital capacity (VC) is not a sensitive marker and usually does not fall below normal limits until there has been a major decline in muscle strength. The VC provides prognostic information. In DMD, reaching the plateau VC phase at an earlier age and a low absolute VC at the plateau phase predicted early

mortality. FVC <1 L was shown to be the best negative predictor of survival in patients with DMD with a median survival of 3.1 years and 5-year survival of only 8% when the FVC fell <1 L.

- Supine VC is more sensitive than upright FVC in detecting diaphragm weakness and has been shown to correlate better with symptoms of nocturnal hypoventilation. A decline of >20-25% is considered an indicator of significant diaphragmatic weakness.
- Lung volumes may reveal a decrease in TLC and increase in RV secondary to a reduced ERV

- Respiratory muscle strength –
 - Maximum inspiratory pressure (MIP or $P_{i_{max}}$), and maximum expiratory pressure (MEP, $P_{e_{max}}$)– As the names suggest, these maneuvers measure the maximum inspiratory and expiratory forces. The accuracy and reliability of these measures remains controversial with values affected by the lung volume at which the lung maneuver is begun, leakage, facial muscle contribution, training, and disparity in published normal reference values. MIP and MEP are useful for excluding weakness if they are normal but can be difficult to interpret if abnormal. In general, a MIP more negative than -70 cm H₂O for women and -100 cm H₂O for men excludes clinically significant weakness.
 - The sniff nasal inspiratory pressure (SNIP) – With this maneuver, one nostril is occluded by a pressure transducer and a sniff maneuver is performed. The SNIP has been shown to be more sensitive in predicting respiratory failure than either FVC or MIP, especially at the later stages of ALS. In general, a SNIP more negative than -50 cm H₂O for women and -60 cm H₂O for men excludes clinically significant weakness.

- CO₂ measurements –
 - ABG – Daytime hypercapnia is a late finding. Once daytime hypercapnia develops in DMD patients, life expectancy without ventilatory support is approximately 9-10 months
 - Other measurements of daytime hypoventilation can include daytime end-tidal CO₂ and transcutaneous CO₂ measures. Elevated serum bicarbonate might suggest hypoventilation.

ii) Cough, airway clearance

- Signs and symptoms of impaired airway clearance include history of pneumonia, and weak and ineffective cough.

- Diagnostic testing:
 - Peak cough expiratory flow (PCEF) – Normal values range from 360-960 L/min. When <270 L/min while healthy, patients are at risk of poor clearance when ill, and <160 L/min at high risk for ineffective cough at any time
 - Maximum expiratory pressure (MEP, $P_{e_{max}}$) – When < +60 cmH₂O, there is a risk of ineffective cough

iii) Swallowing and bulbar function

- Signs and symptoms of impaired swallowing and bulbar function include nasal tonality of the voice, dysarthria, oral accumulation of saliva, impaired gag reflex, dysphagia, weight loss, coughing with drinking and eating, and weak cough.

- Diagnostic testing:
 - Video fluoroscopic swallow study (modified barium swallow), fiberoptic endoscopic evaluation of swallowing

iv) **Sleep-disordered breathing**

The first signs of respiratory insufficiency occur during sleep when skeletal muscle tone is generally decreased, and episodic atony occurs during rapid eye movement (REM) sleep. This leads to arousal, obstructive apneas and hypopneas, sleep fragmentation, poor sleep quality, and, eventually, sleep hypoventilation.

- Clinical evaluation: Frequent nocturnal awakenings, daytime hypersomnolence, fatigue, morning headaches
- Diagnostic testing:
 - In-laboratory polysomnography with CO₂ monitoring – ETCO₂ or transcutaneous
 - Overnight oximetry cannot discriminate between hypoxemia secondary to obstructive apneas and hypoventilation and should be used with caution. The addition of capnography is suggested to improve the detection of nocturnal hypoventilation.

DMD 2004 ATS consensus statement: Objective evaluation at each clinic visit should include

- a. Oxyhemoglobin saturation by pulse oximetry
- b. Spirometric measurements, MIP, MEP
- c. Peak cough flow
- d. Sleep history; Where available annual polysomnography with continuous CO₂ monitoring is ideal
- e. Awake CO₂ tension at least annually. Where available, capnography is ideal for this purpose. ABG analysis is not necessary for routine follow-up of patients with DMD. If capnography is unavailable, a venous or capillary blood sample should be obtained to assess for alveolar hypoventilation.
- f. Annual laboratory studies in patients requiring a wheelchair - CBC, serum bicarbonate concentration

Scenario:

Michael returns to your clinic for follow-up after having completed the requested diagnostic testing:

PFT: FEV1 1.23 (30% predicted), FVC 1.40 (29%), FEV1/FVC 88, MIP -38 cm H₂O (37%), MEP 26 cm H₂O (30%)

PSG: Poor sleep efficiency with prolonged sleep latency, frequent arousals, prolonged REM latency, and decreased REM sleep. There was no snoring. There was a paradoxical movement of the chest and abdomen throughout non-REM sleep. The patient had occasional hypopneas, predominantly in REM sleep. During these events, the chest wall and abdomen were in phase, suggesting they might be non-obstructive. The AHI of 4.2 is normal. Normal oxyhemoglobin saturation. Although no hypoventilation was recorded, the patient rarely achieved a plateau on his CO₂ tracing, raising the possibility that his ETCO₂ measurement was underestimated. TCCO₂ was normal. The periodic limb movement index was normal. No significant cardiac arrhythmias were noted. IMPRESSION: No significant obstructive sleep apnea or hypoventilation, but abnormalities may have been underestimated as REM time was decreased and a CO₂ plateau was rarely achieved

Serum bicarbonate 28

Swallow evaluation: Conclusion: 1. Minimal subepiglottic laryngeal penetration. This is intermittent and is completely extruded from the laryngeal vestibule. 2. Aberrant right subclavian artery impresses posterior wall of upper thoracic esophagus

Question 2: Michael asks about the results. What do you recommend?

Advances in respiratory care have led to a significantly improved outlook in patients with neuromuscular disease, but important available therapeutic interventions are being underutilized.

i) Ventilatory dysfunction

Ventilatory assistance allows patients to extend survival and palliate symptoms. Many patients and families do not receive sufficient information regarding their options for diagnosing and managing respiratory insufficiency.

- *In DMD and ALS, non-invasive ventilation improves survival* (Simonds AK et al. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. Thorax. 1998; Bourke SC et al., Effects of NIV on survival and quality of life in patients with ALS: a randomized controlled trial. Lancet Neurol 2006), improve quality of life, improve symptoms, improve sleep-disordered breathing, improve gas exchange, and slow rate of decline in pulmonary function. NIV is now the preferred modality. In ALS, NIV should be considered to treat respiratory insufficiency to lengthen survival (level B), and may be considered to slow the decline of FVC (Level C) and improve QOL (Level C). Early initiation of NIV may increase compliance (Level C). Bulbar involvement and executive dysfunction may limit a patient's ability to effectively use NIV (2 Class III studies) but this does not mean NIV shouldn't be tried.
- The optimal timing of NIV initiation remains unclear and is in part dictated by reimbursement criteria. As a *general* rule, the most effective time to introduce NIV is when symptomatic sleep-disordered breathing develops. Typically, sleep hypoventilation precedes daytime hypoventilation, and ventilatory support begins with nocturnal non-invasive ventilation with increasing daytime ventilatory support as the neuromuscular disorder progresses. Patients should have regular noninvasive monitoring of gas exchange, including oxygen saturation and end-tidal PCO₂. In Europe, where reimbursement criteria are different (see US criteria below), NIV has been started earlier in the course of ALS with some positive early signals (Vitacca M. et al. Impact of an early respiratory care program with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. Eur J Neurology 2018).

Initial reimbursement coverage criteria for a Respiratory Assist Device (RAD) under Restrictive Thoracic Disorder

Coverage for an E0470 (RAD without a backup rate) or E0471 (RAD with a backup rate) requires criteria A-C

- A. Medical record documentation of a neuromuscular disease or severe thoracic cage abnormality
- B. One of the following:
 - i) A PaCO₂ ≥ 45 mmHg on an ABG drawn while awake and breathing the patient's prescribed FiO₂, or
 - ii) Sleep oximetry done while breathing the patient's usual prescribed FiO₂ demonstrating SpO₂ ≤ 88% for ≥ 5 minutes of nocturnal recording time (minimum recording time of 2 hours), or
 - iii) For neuromuscular disease only, either a maximal inspiratory pressure (MIP) < 60 cm H₂O or a forced vital capacity (FVC) < 50% predicted
- C. COPD does not contribute significantly to the patient's pulmonary limitation

- While NIV is always preferred as the initial step, tracheostomy & invasive mechanical ventilation (IMV) may need to be considered when NIV cannot be used. Situations that may prevent NIV use include bulbar dysfunction, an inability to tolerate noninvasive interfaces, uncontrolled aspiration, or patient aversion to NIV. In ALS, invasive ventilation via tracheostomy is possibly effective in preserving QOL for patients but likely results in a greater burden for their caregivers (2 Class III studies).
- End-of-life care and advanced directives are critical parts of the anticipatory care of individuals with progressive neuromuscular disease. Evidence exists that healthcare professionals treating individuals with DMD underestimate the QOL of ventilator-dependent patients and may use their perceptions of patient QOL when deciding whether to discuss long-term ventilation. Long-term mechanical ventilation should be considered even when the treating physician predicts that the quality of life on long-term ventilation will be poor. The impact of long-term ventilation on the family (including increased financial and care burden) should be addressed. Some experts estimate that the total cost of custodial care for patients with IMV can be approximately as high as \$150,000/year).
- In ALS, there is little data about outcomes after tracheostomy, but some data suggest worse outcomes in patients over age 60, and pneumonia remains a major cause of death despite tracheostomy.

ii) Cough & airway clearance dysfunction

Various techniques have been developed to enhance airway clearance and mobilize secretions. Cough assistance is recommended when clinical history suggests difficulties with airway clearance when the PCEF falls <270 L/min (class III), or MEP <60 cm H₂O

- Cough assist techniques largely assist the clearance of airway secretion from central airways.
- Manual or low-technology techniques include glossopharyngeal (frog) breathing and manual insufflation with a resuscitator (ambu-style) bag, increasing lung volume to achieve better peak cough flow. Additionally, forced exhalation by chest wall or abdominal thrusts timed to a patient's cough can enhance forced exhalation and airway clearance.
 - Mechanical insufflator-exsufflator (MI-E, cough assist) devices simulate cough by providing alternating positive and negative pressure via a face mask, mouthpiece, or tracheostomy. PCEF rates by MI-E have been superior to that generated by manual cough assistance. MI-E requires patient cooperation.
 - Secretion Mobilization techniques can assist with the clearance of secretions from more peripheral airways, including intrapulmonary percussive ventilation (IPV), high-frequency chest wall oscillations (HFCWO), and medications. However, there is minimal data to support these techniques.

iii) Swallowing and bulbar dysfunction –

- Weight loss and muscle mass loss are important drivers of morbidity. A gastric feeding tube (G-tube) effectively prolongs survival in ALS and should be considered to stabilize weight. While there is insufficient data to support or refute the specific

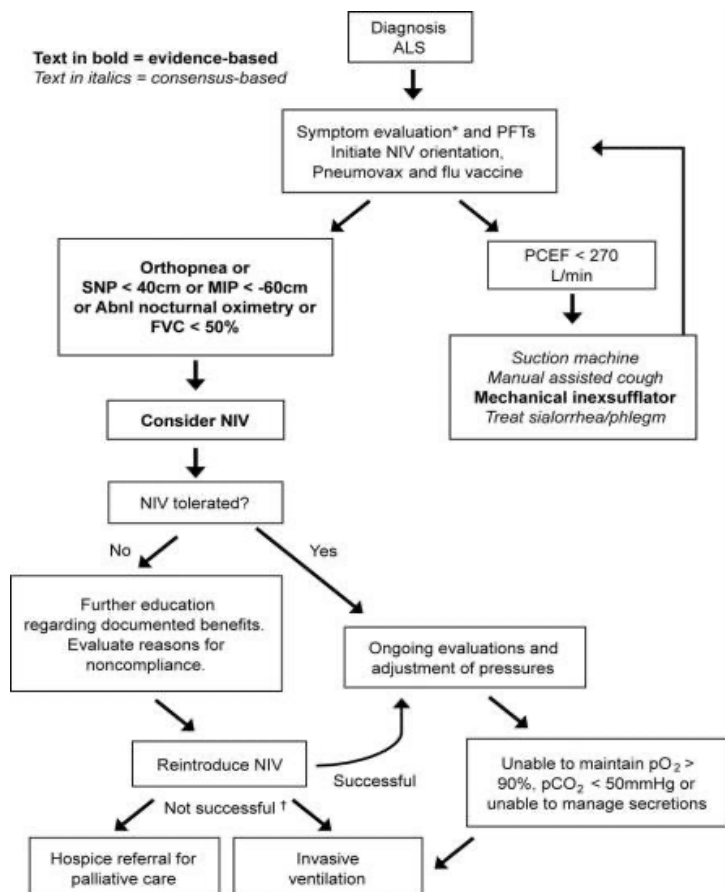
timing of G-tube insertion, the risks of G-tube placement are increased when FVC <50% is predicted and therefore recommended before a decline below this value.

iv) Sleep Disordered breathing –

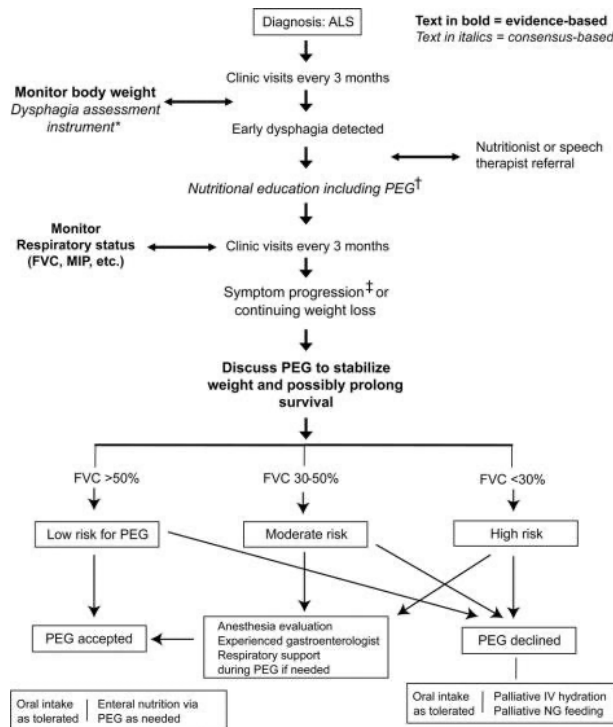
Nocturnal hypoxemia is usually a result of nocturnal hypoventilation and sleep-disordered breathing. Nocturnal bilevel use with a backup rate should be employed as early as possible, generally supported by either polysomnography or the criteria above for respiratory assist devices.

v) Other Considerations

- Patient and care partner education!
 - <https://www.mda.org>- Muscular Dystrophy Association
 - <https://www.als.org>- ALS association.
 - <https://www.als.org/navigating-als/resources/living-als-resource-guides>
- For some disorders, such as DMD, there are significant cardiac comorbidities, and cardiology specialty evaluation is required
- Scoliosis – Nearly all DMD patients develop scoliosis. Failure to repair scoliosis in DMD can result in increased hospitalization rates and poor quality of life, along with worsened respiratory function. The optimal timing for surgery is when lung function is satisfactory.



From: Miller FG et al. Practice Parameters update. The care of the patient with ALS. Neurology 2009

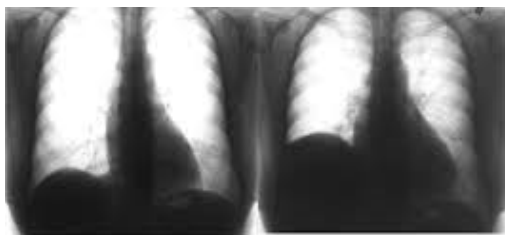


Supplemental Material
(for individual review after the conference or if time permits):

Scenario:

Mr. Jones is a 52-year-old male who presents to your clinic as a new patient for dyspnea. Mr. Jones has a history of hypertension, dyslipidemia, obesity, and atrial fibrillation. He dates the onset of his dyspnea to a pulmonary vein isolation ablation for refractory atrial fibrillation approximately 1 month ago and denies associated cough, chest pains or wheezing. His dyspnea is exertional, especially when trying to swim and positional. He describes orthopnea but denies PND or leg swelling. He was told by his cardiologist his heart was in good shape. On exam, he is seated comfortably, HR 62, BP 148/90, RR 20, SpO2 92% on RA. JVP is flat, heart sounds are regular. There is dullness to percussion on his right lower lung zone with decreased breath sounds and rare crackles. There is no edema or cyanosis.

He brings with him a CXR pre and post-ablation:



Question 3: What diagnosis is suspected? What diagnostic testing do you suggest? What diagnostic studies do you perform?

You suspect a diagnosis of unilateral diaphragm paralysis. The diaphragm is the principal muscle of respiration, innervated by the phrenic nerves that arise from C3-5. Symptoms vary with the degree of dysfunction (weakness to paralysis), laterality, age, and co-morbidities. Patients with unilateral paralysis are usually asymptomatic but coexisting conditions, including obesity, other muscle weakness, underlying heart or lung disease, and/or any process that increases the work of breathing may worsen symptoms. Bilateral dysfunction causes dyspnea (especially positional and immersed in water), sleep fragmentation, hypersomnolence, atelectasis, lower respiratory tract infections, cor pulmonale, and respiratory failure. On physical examination, there may be tachypnea, use of accessory muscles, dullness to percussion, and chest-abdominal wall paradoxical movement.

Diagnostic testing varies with unilateral vs. bilateral paralysis.

- CXR – Elevated hemidiaphragm (unilateral paralysis: sensitivity 90% but specificity 44%), atelectasis
- Fluoroscopy, “sniff test” – Paradoxical cephalad movements of the paralyzed hemidiaphragm, but it is not helpful in bilateral paralysis. False positive 6%
- PFT
 - Unilateral paralysis suggested with TLC 70-79% predicted, while bilateral paralysis is expected to have TLC in the 30-50% range (of predicted)
 - Upright and supine FVC – Normally, the VC falls standing to supine. Allen, Hunt, and Green 1985 showed FVC stand to supine change of 7.5% (SD 5.7) in normal individuals with 95% upper confidence limits for change in FVC 18.9% in normal, suggesting an FVC change >20-25% for diaphragm paralysis, with larger changes expected with bilateral involvement.
 - Maximum static inspiratory pressure, sniff nasal inspiratory pressure – Effort dependent and more variable.
- Ultrasonography of the zone of apposition with the rib cage – There is a lack of thickening with inspiration but it primarily images the central tendon of the diaphragm and not the muscular component and is subject to limitations similar to fluoroscopy.
- Direct measures of diaphragm function
 - transdiaphragmatic pressure (Pdi) – The difference between gastric and esophageal pressure is considered the gold standard.
 - Diaphragm electromyography (EMG) during quiet breathing or phrenic nerve stimulation. There are technical limitations, including proper electrode placement possibility of EMG ‘cross-talk’ for adjacent muscles and subcutaneous fat, but it may help distinguish neuropathic and myopathic causes.

Table 1. Comparison of Bilateral and Unilateral Diaphragmatic Paralysis.*		
Diagnostic Tools and Treatment	Bilateral Diaphragmatic Paralysis	Unilateral Diaphragmatic Paralysis
Presentation	Dyspnea at rest, unexplained dyspnea, exercise limitation, orthopnea, dyspnea when bending, constitutional symptoms, dyspnea when entering water, respiratory failure, prolonged mechanical ventilation	Asymptomatic, unexplained dyspnea; exercise limitation, incidental radiographic finding
History	Neck or shoulder pain, chest or neck surgery, neck injury, manipulation of the cervical spine, neuromuscular disease	Neck or shoulder pain, chest or neck surgery, neck injury, manipulation of the cervical spine, neuromuscular disease
Examination	Abdominal paradox	No abdominal paradox
Laboratory tests		
Vital capacity (% of predicted value)	<50	>70
Decline in supine vital capacity (%)	30–50	10–30
MIP (% of predicted value)	<30	>60
Fluoroscopy	Not helpful	Sniff test positive
Thickening of diaphragm on inspiration†	No change	No change
Pdi max (cm of water)	<40	>70
Twitch Pdi (cm of water)	<20	<10
Complications	Frequent hypoventilation during sleep, atelectasis, pneumonia, respiratory failure	Occasional hypoventilation during sleep, atelectasis
Treatment		
Observation period for recovery (yr)	1.5–3	1.5–3
Treatment for coexisting conditions	Yes	Yes
Reversal of metabolic disturbance	Yes	Yes
NIPPV	Often indicated	Usually not indicated
Plication of diaphragm	Not indicated	May be helpful
Phrenic pacing	Yes, in patients with high SCI	No

* MIP denotes maximal static inspiratory pressure, NIPPV noninvasive positive pressure ventilation, Pdi transdiaphragmatic pressure, Pdi max maximal inspiratory efforts against a closed glottis, SCI spinal cord injury, and twitch Pdi transcutaneous electrical or magnetic stimulation of the phrenic nerve.

† Changes in thickness of the diaphragm are measured with the use of ultrasonography of the diaphragmatic zone of apposition.

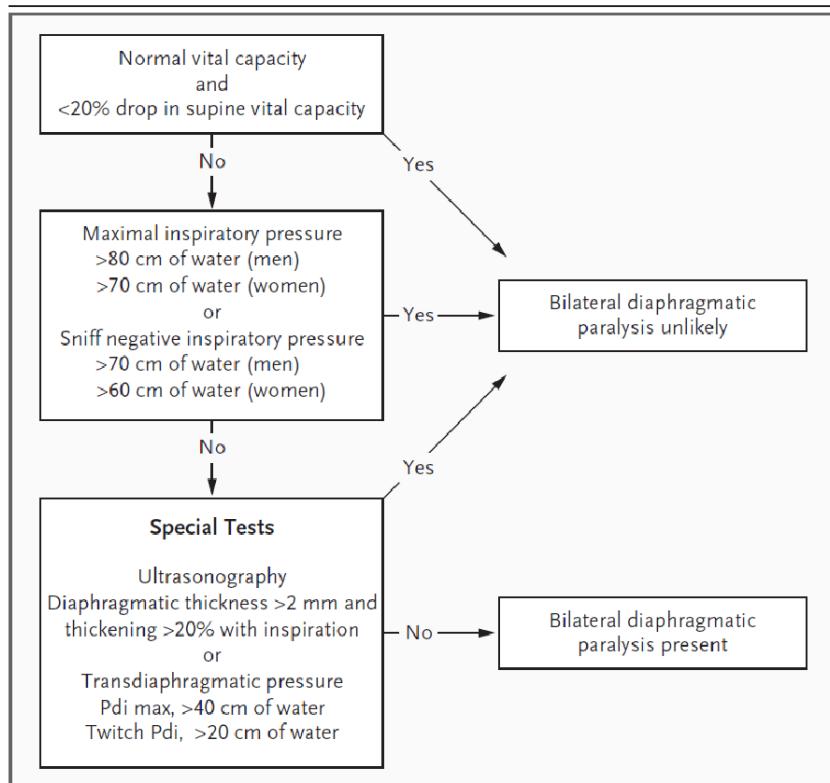


Figure 4. Diagnostic Algorithm for Bilateral Diaphragmatic Paralysis.

This flowchart shows the diagnostic tests that are useful in evaluating whether a patient has bilateral diaphragmatic paralysis. Pdi denotes transdiaphragmatic pressure, Pdi max a Pdi measured during maximal inspiratory efforts against a closed glottis, and twitch Pdi a Pdi measured with transcutaneous electrical or magnetic stimulation of the phrenic nerve.

Figures above borrowed from McCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Engl J Med.* 2012; 366:932-942

Question 4: Sniff confirms the diagnosis of unilateral diaphragm paralysis. Mr. Jones is very upset with his cardiologist. He asks what can be done.

The natural history and treatment of diaphragm paralysis vary depending on the cause. In post-traumatic or infectious causes, spontaneous recovery occurs in approximately 2/3 of patients but may take time. Regeneration of the phrenic nerve, which may take up to 3 years, is necessary for recovery. The prognosis of unilateral paralysis is generally good.

Evaluation and Treatment considerations include:

- For traumatic, post-infectious, and idiopathic causes, clinical observation for 18-36 months will be considered
- Treating other underlying causes, including any intrathoracic obstruction or mass effect from tumors, or effusions.
- Evaluation and treatment for any sleep-disordered breathing
- Evaluation and treatment for systemic neuromuscular disorders for which this might be an initial presentation

Relief of symptoms of dyspnea from diaphragmatic paralysis might include:

- Sleeping in a reclined (wedge pillow) or upright position

- NIV can be very helpful in sleeping supine where they previously were unable to tolerate this position
- Plication can be considered, mostly in unilateral paralysis. Plication is the over-sewing of the membranous central tendon and muscular components to make the hemidiaphragm taut. The indications and timing for plication are not well defined with largely retrospective and uncontrolled studies. It may result in an increase in FVC, FEV1 and TLC of up to 20% and symptomatic improvement but results are significantly better in children than adults. Morbid obesity is a relative contraindication
- Phrenic pacing - potential to provide full ventilatory support for ventilator dependent patients who have bilateral diaphragmatic paralysis but it requires an intact phrenic nerve and normal diaphragmatic motor function

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Pre/Post-Test Questions:

1. You are seeing a 24-year-old male with Duchenne Muscular Dystrophy for routine follow-up. He is currently wheelchair-bound. Which of the following is NOT recommended as part of the routine evaluation of this patient at each clinic visit?
 - a. Sleep history
 - b. Awake arterial blood gas
 - c. Peak cough expiratory flow
 - d. Spirometry
2. On further questioning, you determine that the patient above notes poor sleep quality and frequent morning headaches. His recent chemistry panel is notable for serum bicarbonate of 32, up from 26 a year ago. You are concerned that he may require noninvasive ventilation (NIV) sometime in the near future. Which of the following is true regarding NIV in DMD patients?
 - a. NIV has been shown to improve gas exchange but not survival
 - b. Invasive but not NIV has been shown to improve survival
 - c. NIV has been shown to improve symptoms but not survival
 - d. NIV should be considered in symptomatic sleep-disordered breathing
3. You are seeing a 55-year-old male patient with ALS. You are reviewing his PFTs and another testing, including a sniff of nasal inspiratory pressure. He uses CPAP at night for a history of OSA but has not yet required non-invasive ventilation. He asks you about his likelihood of requiring a tracheostomy for respiratory failure. Which of the following is most sensitive in predicting the onset of respiratory failure?
 - a. A decline in standing to supine FVC >10%
 - b. A reduced maximum inspiratory pressure
 - c. A Sniff nasal inspiratory pressure <40 cmH₂O
 - d. A reduced MVV