Sleep and Neuromuscular Disease Case Study Facilitator Guide

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GR is a 21-year old male with Becker muscular dystrophy who comes to your office complaining of progressively worsening shortness of breath with exertion and rest for the past year. His muscle strength has been slowly weakening over the past year as well, but he continues to be ambulatory and not wheelchair bound.

His mother accompanies him to the visit and reports that he has been more tired recently and gets winded easily with little exertion. They have checked his oxygen saturation at rest and it is usually > 95%.

What are important components of a good pulmonary / sleep history for patients with neuromuscular disease?

A comprehensive medical history, a focused history regarding muscle weakness, and a sleep history are important. The clinical onset of weakness in patients with Duchene muscular dystrophy (DMD) usually occurs between two and three years of age, whereas patients with Becker muscular dystrophy (BMD) typically remain ambulatory until age 15 and some into adult life. Weakness typically affects proximal before distal limb muscles, and lower before upper extremities. It is also important to obtain a thorough history regarding respiratory muscle weakness, including cough strength and the ability to clear secretions. Progression of disease may be indicated by the inability to speak a full sentence without breathlessness, concern for aspiration, respiratory failure, and recurring pulmonary infections. A focused sleep history involves asking about bed times, how long it takes to fall asleep, nocturnal awakenings, how long it takes to fall asleep after awakening, and final wake time. Patients should also be asked about snoring, gasping and choking during sleep, and witnessed apneas. DMD and BMD patients also often have a dilated cardiomyopathy and conduction abnormalities leading to a variety of arrhythmias; therefore a cardiac history is also recommended.

Gardner-Medwin D. Clinical features and classification of the muscular dystrophies. Br Med Bull 1980; 36:109
Bradley WG, Jones MZ, Mussini JM, Fawcett PR. Becker-type muscular dystrophy. Muscle Nerve 1978;1:111
Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol 2010; 9:177
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What measures of pulmonary function are important in this patient population?

Manual or mechanically assisted cough techniques are needed when baseline peak cough flow is < 160L/min or maximum expiratory pressure is < 40cmH20. Recurrent respiratory infections can be present when baseline peak cough flow is < 270L/min. A vital capacity < 30% predicted puts patients at

high risk for hypoventilation. Baseline pulse oximetry < 95% and /or blood or end-tidal CO2 > 45 also puts patients at high risk for hypoventilation. Therefore it is important to obtain baseline and serial measurements of peak cough flow, MIP/MEP, vital capacity, pulse oximetry, and arterial blood gas, to evaluate pulmonary function.

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What questions can be used to better quantify risk of worsening pulmonary function secondary to progressive muscle weakness?

1. Is the patient wheelchair bound?
2. Has the patient had frequent respiratory infections implying inability to cough with adequate force, or aspiration?
3. Is the patient requiring manual or mechanically assisted cough techniques?
4. Is the patient able to speak full sentences without breathlessness?
5. Does the patient have abnormal deglutition due to dyspnea?
6. Does the patient have abnormal oxygenation (pulse oximetry < 95%) or CO2 retention (CO2 > 45mmHg)?

Upon further questioning, GR reports that his baseline pulmonary function tests have started to decline to where his vital capacity is about 40% of predicted. He uses volume recruitment and deep lung inflation using a self-inflating manual ventilation bag twice daily. He has not developed any respiratory infections, and his baseline peak cough flow is > 270L/min. He also reports that he wakes up frequently at night and does not feel well-rested in the mornings. He also is feeling more tired and lethargic during the daytime.

His physical exam is remarkable for blood pressure of 125/75, oxygen saturation of 96% on room air, body mass index of 25kg/m2, Mallampati score of 2, and neck size of 16.5 inches. His respiratory, cardiac, and abdominal exams are normal. He walks upright with a normal gait. He has 4/5 strength in the bilateral lower extremities and 2+ pitting edema of the bilateral lower extremities.

What are the important components of a good physical exam in patients with neuromuscular disease?

Physical exam can suggest increased risk and determine co-morbidities and potential consequences of sleep disordered breathing in patients with neuromuscular disease. It should involve an evaluation of the cardiovascular, neurological, orthopedic, and pulmonary systems. Cardiomyopathy is common in patients with Duchenne and Becker muscular dystrophy. Patients present with a primary dilated cardiomyopathy and conduction abnormalities, and a variety of arrhythmias, primarily supraventricular.

The cardiomyopathy is characterized by extensive fibrosis of the posterobasal left ventricular wall, which can result in significant mitral regurgitation due to involvement of the posterior papillary muscle. This can contribute to symptoms of shortness of breath. Weakness in patients with DMD and BMD affects proximal before distal limb muscles, and lower before upper extremities. In DMD, clinical onset of weakness usually occurs between two and three years of age, and patients are usually wheelchair bound by age twelve. Compared with DMD, the age of onset of symptoms in BMD is usually later and the degree of involvement is milder. The degree of respiratory and nonrespiratory muscle dysfunction may vary among different neuromuscular disease entities, and not all respiratory muscles may be similarly affected. The clinical course may also vary depending on the disease process. Nevertheless, despite the diversity of the underlying condition, the respiratory consequences of severe neuromuscular disease tend to be similar. Orthopedic disorders are also common as patients with DMD often have fractures involving arms and legs secondary to falling. Progressive scoliosis develops in nearly all children with DMD. Scoliosis, in combination with progressive weakness, results in impaired pulmonary function and can lead to respiratory failure. Patients with neuromuscular disease may also have obstructive sleep apnea in addition to hypoventilation, and physical exam should evaluate for physical exam findings that suggest increased risk of sleep apnea such as neck circumference > 17inches in men and >16inches in women, BMI > 30Kg/m2, modified mallampati score of 3 or 4, signs of upper airway narrowing such as a small chin or jaw, and nasal abnormalities.

Perloff JK. Cardiac rhythm and conduction in Duchenne's muscular dystrophy: a prospective study of 20 patients
Sanyal SK, Johnson WW, Dische MR. et al. Dystrophic degeneration of papillary muscle and ventricular myocardium. A basis for mitral valve prolapse in Duchenne's muscular dystrophy. Circulation 1980;62:430
Gardner-Medwin D. Clinical features and classification of the muscular dystrophies. Br Med Bull 1980; 36:109
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Parker AE, Robb SA, Chambers J. et al. Analysis of an adult Duchenne muscular dystrophy population. QJM 2005;98:729
Rodillo EB, Fernandez-Bermejo E, Heckmatt JZ, Dubowitz V. Prevention of rapidly progressive scoliosis in Duchenne muscular dystrophy by prolongation of walking with orthoses. J Child Neurol 1988;3:269
Smith AD, Koreska J, Moseley CF. Progression of scoliosis in Duchenne muscular dystrophy. J Bone Joing Surg Am 1989;71:1066
Oda T, Shimizu N, Yonenobu K, et al. Longitudinal study of spinal deformity in Duchenne muscular dystrophy. J Pediatr Orthop 1993;13:478
Galasko CS, Williamson JB, Delaney CM. Lung function in Duchenne muscular dystrophy. Eur Spine J 1995;4:263

What are symptoms that may point to declining pulmonary function?

1. Weak cough
2. Wheelchair confinement

3. Worsening scoliosis
4. Inability to speak in full sentences without breathlessness
5. Hypersomnolence
6. Difficulty clearing secretions

What is the differential for shortness of breath in this population?

1. Atelectasis
2. Cardiomyopathy with worsening cardiac function
3. Mitral regurgitation
4. Respiratory infection
5. Restrictive lung disease secondary to scoliosis
6. Progressive weakening of respiratory and nonrespiratory muscles

When and how often should you obtain PFTs in this population?

For patients with slowly progressive neuromuscular disease, baseline pulmonary function tests should be obtained prior to wheelchair confinement. In patients with DMD, pulmonary evaluations should be done biannually following wheelchair confinement or vital capacity < 80% predicted.

Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med 2004;170:456

You decide that GR is high risk for pulmonary complications from his neuromuscular disease, and obtain PFTs.

- *PFTs: FEV1 2.03L (88%), FVC 2.26L (69%), FEV1/FVC ratio 90, VC 2.13L (65%), TLC 3.88L (76%), MIP -50, MEP 75*
- *6MWT: Walked 450m with desaturation to 88% and increased heart rate to 130bpm*
- *ABG: 7.40/56/98/34*

When are manual and mechanically assisted cough techniques recommended in this population?

When vital capacity is <40% predicted, volume recruitment/deep lung inflation using a self-inflating manual ventilation bag or mechanical insufflation-exsufflation is recommended. Manual and mechanically assisted cough techniques are recommended when respiratory infections are present and baseline peak cough flow is <270L/min, or when baseline peak cough flow is <160L/min or MEP is < 40cmH20, or when baseline vital capacity is <40% predicted or < 1.25L. Use of lung volume recruitment and assisted cough techniques should always precede initiation of noninvasive ventilation.

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When should we consider nocturnal ventilatory assistance?

1. When vital capacity is <30% predicted as patients are at especially high risk for hypoventilation, or
2. When baseline pulse oximetry is <95% and/or blood or end-tidal CO2 is > 45mmHg while awake, or
3. When on polysomnogram, the apnea-hypopnea index is >10 per hour, or there are four or more episodes of pulse oximetry <92%, or there are drops in pulse oximetry of at least 4% per hour of sleep

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What test could be ordered to evaluate patient's need for nocturnal ventilation?

An overnight attended polysomnography (PSG) should be ordered to evaluate patient's need for nocturnal ventilation. A polysomnogram records physiologic variables during sleep using electroencephalogram (EEG), electrooculography (EOG), chin electromyography (EMG), electrocardiography (ECG), airflow, oxygenation, snoring, respiratory effort, and leg (anterior tibialis) EMG. PSG would reveal nocturnal hypoventilation, hypoxemia, and the presence of sleep apneas. Patients with neuromuscular disease should also have a measure of carbon dioxide (CO2) during PSG. Two noninvasive surrogate measures that have been widely adopted for use during PSG are: end tidal CO2 capnography (ETCO2), or transcutaneous CO2 measure (TCCO2). ETCO2 capnography uses a nasal sampling interface. ETCO2 monitors reflect the CO2 present and detected in exhaled air. The highest concentration of CO2 is present at end exhalation, which is the number reported by ETCO2 monitors. The normal ETCO2 is between 35-45mmHg. A high ETCO2 reading in a neuromuscular patient suggests hypoventilation and a possible need for nocturnal noninvasive ventilation. One disadvantage of ETCO2 is it may underestimate CO2 in patients with chronic lung disease because of a mixture of alveolar gas with gas from physiologic dead space. As the ETCO2 monitor uses a nasal sampling interface, its accuracy is inconsistent under conditions in which supplemental oxygen or positive airway pressure is being used, and in patients who are "mouth breathers". TCCO2 utilizes an electrode with a fixation ring applied to the skin surface (often inner thigh). This interface may sometimes produce cutaneous irritation. TCCO2 is particularly useful for patients with moderate to severe airway obstruction, or increased physiologic dead space in whom ETCO2 may underestimate CO2. TCCO2 monitoring may not be reliable in patients

with perfusion problems, skin diseases, edema, or hypovolemia. In pediatric populations, some studies have shown that TCCO2 may overestimate CO2 during hypercarbia.

Morielli A, Desjardins D, Brouillette R. Transcutaneous and End-Tidal Carbon Dioxide pressures should be measured during pediatric polysomnography
Kirk V, Batuyong E, Bohn S. Transcutaneous Carbon Dioxide monitoring and capnography during pediatric polysomnography

You are concerned regarding nocturnal hypoventilation and hypoxemia and request an in-lab attended polysomnogram. The sleep study report is as follows:

- *Sleep Architecture: Exam started at 2022 and ended at 0440. Sleep latency was 25mins, and REM latency was 90mins. Sleep efficiency was 85%. Patient had normal distribution of stage N1, N2, N3, REM. He had 236 arousals during the exam.*
- *Respiration: AHI was 15/hr and there was evidence of hypoventilation with the average event lasting 33 seconds with a maximum duration of 62 seconds. Episodes of hypoventilation were worse during supine REM.*
- *Oxyhemoglobin saturation: Mean oxyhemoglobin saturation was 96%. Oxyhemoglobin saturation was below 88% for 20 minutes. Nadir oxygen saturation during episodes of hypoventilation was 75% on room air.*

What tests are available to diagnose hypoventilation syndrome associated with neuromuscular disease?

In lab attended polysomnogram should be used to diagnose hypoventilation syndrome associated with neuromuscular disease. In the absence of polysomnogram, representative markers of disease severity such as vital capacity <30% predicted, baseline pulse oximetry < 95% or end tidal CO2 > 45mmHg while awake may be used. Additionally, symptoms of morning headaches and hypersomnolence may also be used to suggest hypoventilation and prompt further testing. Medicare guidelines for initiating noninvasive nocturnal ventilation in this population are
1. Documentation in medical record of progressive neuromuscular disease, and
2. Arterial blood gas sample done on patient's usual FiO2 of PaCO2 >45mmHg, or sleep oximetry demonstrating desaturation of ≤88% for ≥5 minutes on patient's usual FiO2, or MIP <60cmH20 or FVC <50% predicted, and
3. Chronic obstructive pulmonary disease does not contribute significantly to the patient's pulmonary limitation

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How should sleep disordered breathing be treated in this population?

Sleep disordered breathing should be treated with continuous positive airway pressure (CPAP) when the AHI is >10 per hour on polysomnogram, or there are four or more episodes of desaturation with pulse oximetry < 92%, or there are drops in pulse oximetry of at least 4% per hour of sleep. Patients with signs of hypoventilation such as baseline pulse oximetry < 95% and/or end tidal CO2 > 45mmHg while awake, should be treated with noninvasive ventilation.

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Based on the results of the polysomnogram, you make treatment recommendations.

What treatment options are available for nocturnal hypoventilation and hypoxemia in neuromuscular patients?

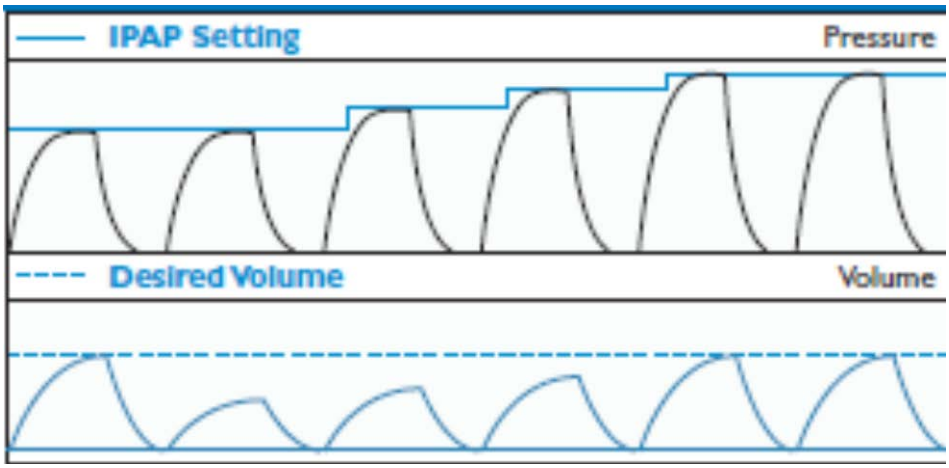
Bilevel positive pressure (BPAP) machines provide non-invasive ventilator support that resembles pressure support ventilation on hospital ventilators. They have flow triggers for cycling between inspiratory and expiratory pressures. This allows for matching of the patient's breathing efforts closely; most also provide a time-cycled backup mode.

Average volume assured pressure support (AVAPS) is approved for patients with chronic hypoventilation such as neuromuscular disease. It is a hybrid that combines pressure-limited and volume-limited modes of ventilation into one ventilation mode. It ensures a more consistent tidal volume while providing the comfort of pressure support ventilation. Based on an internal algorithm, AVAPS estimates the patient's tidal volume with each breath and compares it with the target tidal volume. When needed, the algorithm slowly increases or decreases inspiratory pressure (IPAP) for each breath in order to achieve the preset tidal volume. AVAPS delivers pressure changes progressively, allowing patients to tolerate the pressures better while the target tidal volume is reached, compared to the set pressures from BPAP. Another mode of ventilation that is routinely confused with AVAPS is adaptive servo-ventilation (ASV). ASV is the preferred therapy for patients with hyperventilation related central sleep apnea (Cheyne-Stokes breathing, or high altitude periodic breathing) who have failed CPAP. ASV provides variable inspiratory pressure superimposed on EPAP, with a backup respiratory rate. The magnitude of inspiratory is reciprocal to the amount of respiratory effort.

When ordering AVAPS, one will need to set the tidal volume desired (generally 8ml/kg ideal body weight), the maximum IPAP (25cmH20 is the maximum that the machine will achieve), the minimum IPAP (suggested by the company to be EPAP + 4cmH20), the expiratory positive airway pressure (EPAP)

based on the presence of obstructive apneas, the respiratory rate (generally 2-3bpm below resting respiratory rate), the inspiratory time, and the rise time for patient comfort. Alternatively, BPAP S/T only allows variation in the back up rate, maximum IPAP, and EPAP.

Small studies comparing BPAP S/T (BPAP with backup rate) to AVAPS have shown that patients on BPAP S/T alone remained hypercapneic overnight, whereas patients on AVAPS had normalization of mean transcutaneous PCO2 during sleep. Additionally, the leak with AVAPS may be lower than that with BPAP S/T at higher pressures, allowing for more effective ventilation.



Schematic of progressive change in IPAP for each breath (0.5 to 1cmH20/min) in order to achieve preset tidal volume. www.healthcare.philips.com

Claudett K, Claudett M, Wong C, et al. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. BMC Pulm Med 2013; 13:12
Storre J, Seuthe B, Fiechter R, et al. Average Volume-Assured Pressure Support in Obesity Hypoventilation. CHEST 2006; 130:815-821

What precautions have to be taken with use of noninvasive positive pressure ventilation (NIPPV) in these patients?

Most patients with progressive neuromuscular disease may eventually require noninvasive positive pressure ventilation, either nocturnal or all day. It is important to ensure that patients are appropriate and safe candidates for noninvasive ventilation. Nocturnal noninvasive ventilation should not be used for neuromuscular patients with acute respiratory failure. These patients need to be admitted to the hospital for evaluation for invasive ventilation. Patients with neuromuscular disease who are on noninvasive ventilation should have a caregiver present whenever noninvasive ventilation is in use. This is to ensure that patients are able to receive timely and appropriate help with mask removal if they encounter complications such as vomiting, aspiration, difficulty with secretion clearance, or the inability

to protect their airway while on noninvasive ventilation. Various combinations of noninvasive ventilation, manually assisted coughing, mechanically assisted coughing with insufflation/exsufflation devices, and glossopharyngeal breathing are available to promote secretion clearance in this population.

Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AIDS. Chest 2002; 122:92
Bach JR. Update and perspective on noninvasive respiratory muscle aids. Part 2: The expiratory aids. Chest 1994;105:1538
Boitano LJ. Management of airway clearance in neuromuscular disease. Respir Care 2006;51:913

After some discussion GR accepts your recommendations and opts to use AVAPS. You arrange for an in-lab AVAPS titration to ensure that he is titrated to comfort and doesn't have a mask leak.

GR returns 1 year later – he continues to use nocturnal AVAPS and feels like his sleep has improved. However, he complains that he thinks his disease has progressed and he is now getting breathless just with talking. On exam, his oxygen saturation at rest is 91%.

When would you recommend daytime ventilation?

Daytime ventilation can be the self extension of nocturnal ventilation into waking hours. It is indicated as the disease and weakness of respiratory and nonrespiratory muscles progress. One indication for extension of nocturnal ventilation into waking hours is the inability to speak a full sentence without breathlessness, and/or symptoms of hypoventilation with baseline pulse oximetry < 95%, or an end-tidal CO_2 > 45mmHg while awake. It also may be used for patients who have abnormal deglutition due to dyspnea that is relieved by ventilator assistance. Continuous noninvasive ventilation with mechanically assisted cough may also facilitate extubation for patients endotracheally intubated during an acute illness or during anesthesia.

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What are the guidelines regarding tracheostomy placement in these patients?

In patients whose respiratory insufficiency is not adequately treated with noninvasive ventilation, the clearest indications to transition to invasive ventilation are failure to maintain adequate oxygenation, acute respiratory acidosis, and inability to adequately protect the upper airway due to impaired swallowing, cough, excessive secretions, or a combination of the above. Other indications include multiple failures to achieve successful extubation during critical illness despite optimum use of

noninvasive ventilation and mechanically assisted cough. The decision to switch from noninvasive to invasive ventilation depends largely upon patient preference. Most patients are reluctant and would favor remaining on noninvasive ventilation as long as possible.