a cure is among us

CMD PULMONARY GUIDE

for affected individuals, families and clinicians

LEARN ABOUT PROACTIVE PULMONARY CARE

Respiratory symptoms in congenital muscular dystrophy are perhaps the most critical in maintaining overall health. Please share this guide with your healthcare team to ensure you are receiving optimized, proactive pulmonary care.

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Respiratory Natural History in CMD

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Musculoskeletal Respiratory Physiology

While the lungs are at the core of the respiratory system, lung function is largely dependent on the integrity and complex dynamics of the supportive thoracic skeleton, articulating joints and the muscles of respiration. The ribs, sternum and spine largely determine the static resting thoracic volume; however, it is the respiratory muscles that determine the dynamic thoracic volume seen during respiration.

For inspiration, the central muscle in this is the diaphragm, which contracts downward and rotates the lower edge of the ribcage outward to increase the chest wall circumference and progressively decreased intrathoracic pressure pulling air into the lungs. The downward motion of the diaphragm is determined by the extent of the curve of the diaphragm and then the vertical portion aligned along the circumference of the lower edge of the rib cage, the area of apposition. So the more curved the diaphragm is and the larger the area of apposition is, the more the diaphragm can contract downward and the deeper one can inhale. Then the pectoral and neck muscles can elevate the rib cage outward further. While restful exhalation through tidal range is based on passive recoil of the lungs, a forced exhalation as with coughing or deep breathing involves activation of the rectus abdominis and abdominal oblique muscles to forcefully exhale.

The spine provides the general infrastructure of the thorax to maintain an erect posture, while the ribs provide the span or breadth with articulating joints kept aligned by ligaments to make the costa-vertebral unit dynamic. The perispinal, back, intercostal and abdominal muscles then work in concert to keep the ribs and spine in the optimal position to allow the diaphragm to contract efficiently and then the chest wall to expand outward as fully as possible during respiration. However, to the extent that this does not happen, muscles will not work well and there can be an additional load on the respiratory system that can further tax weak respiratory muscles.

Respiratory Pathophysiology

The effectiveness and efficiency of inspiration is determined by the extent of diaphragm contraction against the load of moving the respiratory system to allow the lungs to expand. The normal load is the weight of the chest wall, including ribs, muscle and additional soft tissue, and resistance of moving the ligaments around the costovertebral joints. Many of the subtypes of CMD are associated with substantial joint contractures, and the intrinsic collagen abnormality in Collagen VI-CMD can make ligaments stiffer and less elastic thereby causing external restriction.

Therefore, it is certainly easy to understand how a weak diaphragm can produce respiratory dysfunction by decreasing the depth of breathing. However, a poorly oriented diaphragm with a larger radius of curvature, or flatter, will not contract downward or expand the lower edge of the rib cage as well. In this situation, breathing will be shallow and to ventilate properly the affected individual will compensate by breathing more rapidly in a rapid-shallow breathing pattern.

In neuromuscular disease, weak paraspinal and abdominal muscles can make the spine and chest wall unstable and produce a scoliosis. In addition, there is a caudal rotation of the ribs in on the convex side and compression of the ribs on the concave side of the chest. Since most scoliosis will occur with spinal rotation there can also be a torsional effect that may alter diaphragm orientation and negatively impact contractility. Finally, there can also be alterations in the sagittal plane with either a kyphotic curve, broadening of the front to back (anteroposterior AP) diameter, or excessive lordosis narrowing the AP diameter.

These deforming stresses can both alter diaphragm orientation by changing the relative location of the diaphragm insertion points and limit downward motion of the diaphragm. In addition, the rotational or torsional stress from scoliosis and the kyphosis displacing the diaphragm anteriorly can flatten the diaphragm and limit downward motion. In addition, this can place the diaphragm muscle fibers horizontally and pull the lower edge of the rib cage in as opposed to expanding it outward.

Finally, with progressive decreased motion of the thorax, the costal vertebral joints will progressively ankylose and the intercostal muscles can atrophy and become fibrotic, thereby making the thorax less compliant and harder to move during respiration and decrease lung volumes especially during deep breathing.

The reduction in dynamic volumes is exaggerated during sleep, and especially so during REM (dream) sleep when there is global reduction of muscle tone. During phasic REM sleep, affected individuals are most vulnerable due to the lack of rib cage contribution to tidal volume.[1] As a result, there is hypoventilation (under ventilation) causing increased carbon dioxide and eventually low blood oxygen levels. With disease progression this will occur in less deep non-REM sleep and eventually during awake time.

Respiratory failure and the timing at which this occurs is dependent on the balance of respiratory muscle strength with the force needed to move the respiratory system. The simple principle is that while weak respiratory muscles may work against a modest load and strong respiratory muscles may work against a heavy load, weak muscles working against a heavy load will quickly lead to muscle failure. The challenge is to proactively follow the loss of function both clinically and objectively to determine when and then how to intervene to properly support the muscles ultimately the affected individual.

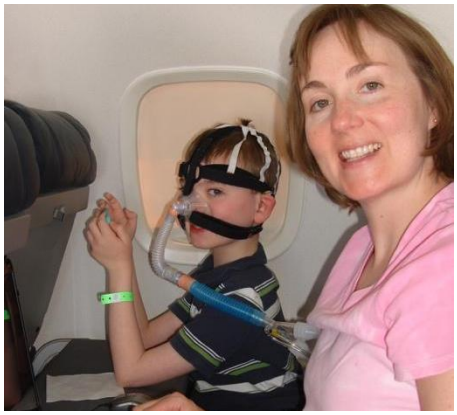
Respiratory Time Points

While the natural history of respiratory decline in the congenital muscular dystrophies is variable, the pulmonary function changes are similar. As the respiratory muscles weaken, the force that can be generated to move the respiratory system declines and as this occurs the lung volume moves during breathing and the speed of exhalation (flow) will decline. With loss of muscle strength and lung volume comes clinical challenges such as problems with airway clearance and inhaling oxygen (oxygenation) and exhaling carbon dioxide (ventilation). Therefore, there are three overlapping sequential phases of decline: muscle function, lung volume/flow, and need for mechanical ventilation.

There are a variety of different pulmonary function outcomes that can be used to assess respiratory status, but some of these are limited by the age range at which they can reliably be performed. The only exception to this is assessment of respiratory failure by polysomnography (sleep study), which can be performed at any age. The standard techniques for respiratory muscle assessment, lung volume and flow measurement are applicable to school age children and older, but most cannot be modified for use

in a younger age population. This is highly problematic in making an accurate objective functional assessment and identifying the initiation of respiratory decline. The more subjective solution that is applicable across the age spectrum is a clinical assessment, which is of course then dependent on the skill and expertise of the clinician. Specific techniques for pulmonary function and clinical assessment are discussed in detail later in this document.

Specific Pulmonary Outcomes in CMD Subtypes



The respiratory morbidity relative to pulmonary function is fairly well correlated and described in Duchenne muscular dystrophy, but is not nearly as well described in the CMD subtypes.

There was a large international study evaluating all available subjects with collagen-6 myopathy.[2] In examining the entire group there was a 0.9% annual rate of decline in forced vital capacity as a percentage of predicted (FVC%).[2] However, in examining affected individuals with the more severe Ullrich phenotype (non-ambulant) there was a higher (2.6%) annual rate of decline of FVC%.[2] Interestingly, in the least severe Bethlem phenotype, there was no significant decline in FVC% and in the intermediate phenotype in which the affected individuals obtained ambulation, there was a similar rate of decline in FVC% (2.3%) to the Ullrich subtype.[2] The Ullrich and intermediate subtypes differed in the mean onset of chronic respiratory failure and initiation of non-invasive ventilation NIV (11.3 vs 20.7 years).[2] In examining the progression of FVC% based on the maximal level of physical function attained, there was a progressive increase in the rate of decline of FVC% going from subjects able to run, walk, walk with assistance, and sit.[2]

In a smaller single center study of 13 subjects with Ullrich CMD, the mean age of starting non-invasive ventilation (NIV) was 14.3 years and a rough correlation with a FVC% predicted of 20%.[2] In both studies, by the time there was reportable FVC% in affected individuals with Ullrich CMD at 6 years of age, the FVC% was already low (< 80%).[3]

In LAMA2 (merosin deficient) CMD there are less data; however, in a single center that was a major international referral center for CMD, the authors reported on 46 subjects, 33 of whom had a more severe phenotype.[3] Though they did not report the FVC%, they did report that there was a greater percentage of the more severe subjects requiring NIV, in whom there was no residual merosin staining on biopsy, than in those with residual merosin (39.3% vs. 7.6%).[4]

The general principle in progressive loss of respiratory function in neuromuscular disease is that loss of ambulation occurs in the midst of loss of pulmonary function and before the onset of chronic respiratory failure and the need for NIV. This principle is violated in SELENON (SEPN1)-Related Myopathy, where not only is there a poor correlation between progressive loss of FVC% and the need for NIV, but in one report of 11 subjects, of the 4 subjects requiring NIV, all of them were still ambulatory.[5]

In a separate study of seven affected individuals with SELENON (SEPN1)-RM, 5 of 6 pediatric affected individuals required nocturnal ventilation while still ambulatory, based on clinical assessment and not on FVC.[6] Interestingly, 3 of the 5 affected individuals able to perform sitting and supine pulmonary function testing had a >20% decline in FVC, indicating diaphragm weakness.[6] Separate from FVC%,

there was severely reduced diaphragmatic function, based on direct diaphragm contractility measurements, in 4 of 7 subjects.[6]

Summary

1. The changes in the respiratory status in patients with CMD follow a largely consistent pattern irrespective of CMD subtype.
2. While there are important clinical signs and pulmonary functional outcomes that can correlate with loss of function, it is critical to be aware of small changes in overall status and address them with the medical team in between medical visits.
3. Because there are treatments that can support loss of function, understanding the progression of the CMD subtype is critical in knowing what signs to look for and then when to start supportive therapy as close to the time of first need as possible.

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Pulmonary Function Testing

MyMy Buu, MD | Oscar Mayer, MD

Introduction

While the congenital muscular dystrophies (CMD) are heterogeneous disorders with distinct genetic causes and phenotypes, the respiratory complications of these disorders overlap and lead to progressive, restrictive respiratory insufficiency. Restrictive respiratory insufficiency is a result of abnormal chest wall compliance, weak inspiratory and expiratory muscles, resulting in abnormal pulmonary function (Table 3.1). Abnormal chest wall compliance and spinal support causes chest wall deformity, scoliosis, restrictive respiratory defect and respiratory insufficiency. Weak inspiratory muscle strength leads to ineffective airway clearance and recurrent respiratory infection.

Table 3.1 Respiratory complications of neuromuscular disease.

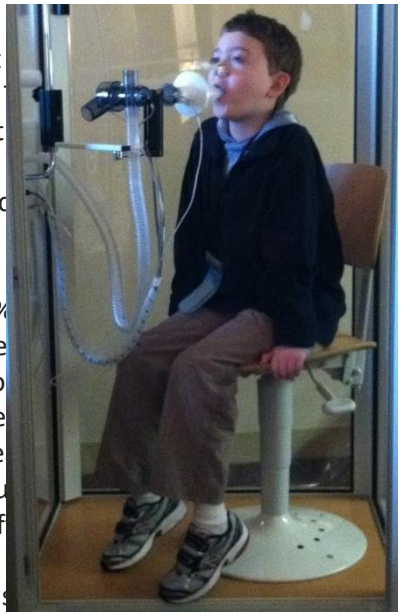
Abnormality	Clinical Sequela	Measurement of Lung Function
Abnormal chest wall compliance	Chest wall deformity Scoliosis	Vial capacity, sitting and supine
Weak inspiratory muscles External & internal intercostals Diaphragm	Low lung volumes Insufficient ventilation	Maximal inspiratory pressure
Weak expiratory muscles Diaphragm Internal intercostals Abdominals Quadratus lumborum	Ineffective airway clearance Recurrent respiratory infections	Maximal expiratory pressure Peak cough flow

Lung volumes, muscle strength, and cough strength are important to measure and track longitudinally in order to accurately detect the onset of respiratory insufficiency and help to determine when intervention might be necessary. In addition, accurate measurement of pulmonary function is also important to assess efficacy of therapies, such as in clinical trials. Pulmonary function testing available in clinical settings include spirometry for vital capacity (VC), tests of respiratory muscle strength including maximal inspiratory and expiratory pressure (MIP, MEP), and peak cough flow (PCF). Other complementary tests of pulmonary function include resting lung volume functional residual capacity (FRC) by helium dilution technique (FRC) and sniff nasal inspiratory pressure (SNIP), which is often used in place of MIP since the sniff is a more natural breathing maneuver than breathing against a closed shutter as with MIP.

As is the case with every measure of muscle function, measurements of maximal volume, flow and pressure, require maximal effort and to the extent that maximal effort is not given, the results will reflect true pulmonary function. Acknowledging this, modifications to the widely used American Thoracic Society Guidelines for performing spirometry have been proposed for use in affected individuals with neuromuscular disease.[1]

Vital Capacity

Vital capacity is a measure of the total volume of air that an affected individual can move through his or her lungs after a full, deep inspiration and a complete exhalation, and as such it is an integral measure of pulmonary function, including both inspiratory and expiratory muscle function. It is the most commonly used outcome measure in both clinical and research testing. T longitudinal trend of VC was discussed in the section on Respiratory Nat History. Different rates of decline in VC have been described in affected individuals whether they are walking (0.6%/year), walking with assistanc (2.1%/year), or sitting (4.2%/year) at the time of measurement [2].



In Duchenne Muscular Dystrophy, differences in VC of greater than -20% between the sitting and supine position and sitting VC less than 60% pre been associated with nocturnal hypoventilation;[3] however, the relatio between VC and hypoventilation is not well described in the CMD's. The degree of change in sitting and supine VC is felt to reflect diaphragm we a study of 51 individuals with COL6-RD and LAMA2-RD, affected individu COL6-RD have significant differences in sitting and supine VC because af individuals with COL6-RD affected individuals are likely to have more diaphragmatic involvement [1]. This is in contrast to affected individuals LAMA2-RD who did not have a significant difference between sitting and supine VC [5]. Interestingly, in this study, the difference in sitting and supine VC did not differ by whether or not the affected individual was supported by NIV for more or less than 16 hours, nor was it different between ambulant and non-ambulant subjects.

When performing VC as part of a spirometry maneuver, a number of other results are produced. The forced expiratory volume in the first second of exhalation (FEV1), the forced expiratory flow between 25% and 75% of vital capacity (FEF25-75%) and the ratio of FEV1/FVC are also produced. While the FEV1 is often associated with obstructive lung disease when it is only 80% or less of VC, FEV1/FVC below 0.80, when there is no obstruction, as is often the case in CMD, it can be used as a surrogate for VC.[6] The FEF25-75% is a measure of expiratory flow that is typically well preserved in patients with neuromuscular disease as VC begins to decline, it eventually declines. Based on this relatively late change it is obviously not useful in identifying early respiratory difficulty in patients in neuromuscular disease.

Maximal Expiratory Pressure and Maximal Inspiratory Pressure

Maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) are straight-forward tests to perform, but can be variable because of the maximal effort needed to perform accurate testing.[7] MIP involves inhaling with maximal effort against a closed shutter from the point where the lungs are empty (residual volume). In measuring inspiratory muscle strength, it primarily measured diaphragm function. MEP involves exhaling with maximal effort after a full inspiration (total lung capacity). As such it measures expiratory muscle strength, or primarily abdominal muscle function. The pressure recorded is the maximal sustained pressure for a second, which makes the testing challenging to perform for an affected individual with respiratory muscle weakness.

While a normal value can be reassuring, if low, it is hard to know whether a low value reflects respiratory muscle weakness, poor effort, fatigue, or difficulty obtaining a good mouth seal [8]. MEP and

MIP have been measured in affected individuals with neuromuscular disease as signs of respiratory impairment or diaphragmatic weakness [8, 9]. Normal values and natural progression of decline has not been described in affected individuals with CMD.

Peak Cough Flow

Peak cough flow (PCF) is the maximal flow produced during a cough maneuver involving both a deep inspiration and a forceful exhalation with full effort. It has been proposed as a measure to assess cough efficacy with a value of < 270L/min is felt to foreshadow inadequate airway clearance during an acute respiratory illness [10]. In affected individuals with neuromuscular disease, PCF can improve by up to 30 L/min after a session of mechanical insufflation-exsufflation using a Cough Assist® device [4].

Assessment of pulmonary function is especially important in CMD due to the large clinical variability of the diverse subtypes. Measurements of lung volumes and muscle strength are important to detect onset of respiratory compromise and document effectiveness of respiratory therapies and disease modifying therapies. Both volitional and non-volitional measurements of pulmonary function should be considered. There has been an emphasis to develop and characterize pulmonary function measurement and techniques for young affected individuals (less than 6 years of age) for both clinical care and clinical trials.

Summary

1. Routine pulmonary function testing a critical part of a comprehensive assessment of overall respiratory status in patients with CMD.
2. The three main outcomes are volume of air exhaled, the pressure that the breathing muscles can produce, and the flow of exhaled air that the breathing muscles can make.
3. Each test of pulmonary function requires maximal and reliable effort in order to produce accurate data.
4. Pulmonary function testing data are critical in following changes in function over time and also identifying when additional therapies might be necessary.

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Assessment for Nocturnal Hypoventilation and Sleep Disordered Breathing

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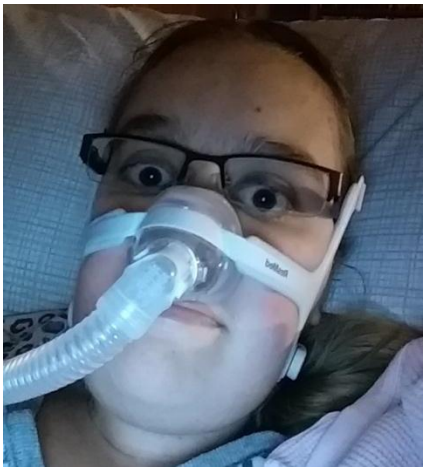
Sleep-Disordered Breathing



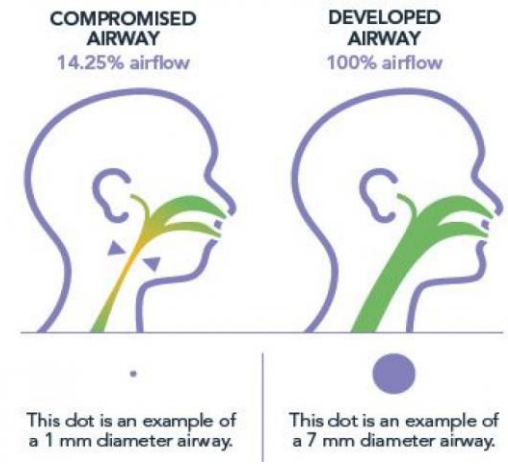
The pathologies of respiration encountered during sleep in the CMD's are variable and poorly characterized or described. Changes in respiratory patterns and the onset of hypoventilation are directly related to muscle weakness. As mentioned earlier, there is an increased respiratory load due to the low compliance (stiffness) of the chest wall and eventually the lungs become poorly compliant due to loss of lung volume. This increased respiratory load then is balanced by the respiratory pump, or muscles, of which the diaphragm is the most important. Respiratory motion or ventilation is determined by how well the diaphragm overcomes this load.

In sleep, and especially in deep REM sleep, the respiratory muscles relax and chest wall motion may decrease as a result. Normally, there is a mild elevation of 2-4 mmHg in carbon dioxide levels after a person first falls asleep. This is the normal result of reduced tidal volume,[1] reduced respiratory rate,[2] reduced sensitivity of central chemoreceptors that would normally stimulate increased respiration.[3] In early stages of respiratory failure, affected individuals manifest frequent nocturnal awakenings (sleep disruption) as their tidal volumes reduce further and carbon dioxide levels increase, even though these increases may not yet be considered abnormal. Poor sleep quality with frequent awakenings is a common complaint at this stage. This leads to a progressive increase in respiratory rate in order to ventilate better and maintain normal carbon dioxide levels. The elevations in carbon dioxide levels may occur in the absence of apneic events (no air flow), making these phenomena very different from those described in Duchenne muscular dystrophy, where there can be a component of obstructive apnea.[4]

On polysomnographic (sleep study) tracings, these shallow breaths are non-obstructive reductions in airflow (hypopneas) and can indicate respiratory muscle fatigue, the first step in developing respiratory failure. Different respiratory muscle groups are variably sensitive to the muscle inhibition seen during REM sleep. The diaphragm is the only respiratory muscle that does not become hypotonic during REM-sleep. As a result, the diaphragm becomes the primary respiratory muscle during REM-sleep while the intercostal and accessory muscles contribute to maintain rib cage stability only during non-REM sleep. Therefore, respiratory motion during REM-sleep is predominantly dependent on diaphragm function, and diaphragmatic weakness can produce substantial hypoventilation during REM sleep. There are types of CMD (SEPN-1 related myopathy) in which there is selective diaphragm weakness.

Nocturnal hypoventilation results from the combined effects of reduced supine lung volumes, reduced chest wall motion, reduced central sensitivity to carbon dioxide levels (ventilatory response), and reduced tidal volumes. Alveolar hypoventilation in children is defined as when 25% of the total sleep time is spent with carbon dioxide levels greater than 50 mmHg.[5] However, by the time affected individuals achieve this degree of abnormality, they have usually begun to experience hypoventilation

while awake. Another limitation of this definition is that it fails to take into consideration compensatory mechanisms to maintain normal carbon dioxide levels, such as increasing respiratory rate. In children, a more liberal definition is greater than 2% of total sleep time with carbon dioxide levels greater than 50 mmHg.[6,7]



Nocturnal oxygen desaturation can occur because of hypoventilation and high carbon dioxide levels and/or low lung volumes due to shallow breathing with collapse of segments of the lung (atelectasis).[8] Polysomnography plays a very important role in the evaluation and management of individuals with neuromuscular weakness. It is well accepted that respiratory abnormalities during sleep are poorly identified using sleep history, sleep diaries and assessing sleep hygiene. The American Academy of Sleep Medicine (AASM) supports routine polysomnography evaluation in the presence of an underlying neuromuscular diagnosis.[9] Polysomnography evaluation allows for the early identification and diagnosis of sleep disordered breathing, and initiation of ventilator support.

The goals of ventilator support are to correct both elevated carbon dioxide and low oxygen and improve sleep and quality of life. The ideal approach to initiating ventilation is in a monitored setting in a sleep laboratory or in an inpatient hospital setting. Initiation of ventilation not only involves selecting the proper settings, but also identifying appropriately fitting masks, making sure that it is comfortable and ensuring that there are no air leaks from under the mask. This is best done using experienced care providers. More detail on the process of initiating ventilation will be in the section on Chronic Ventilation.

Although polysomnography is available at most pediatric hospitals, the experience in identifying subtle abnormalities indicating the early stages of hypoventilation is challenging and can be missed by practitioners not experienced in neuromuscular disease. It is also critical to have a polysomnography study performed with a reliable continuous carbon dioxide tracing; without this, there is no way to accurately evaluate for hypoventilation, which is the critical component of a study in a CMD affected individual. Without both the understanding on how to evaluate a polysomnography study in an affected individual with neuromuscular weakness or a carbon dioxide reading, there is a high risk of a study being misinterpreted.

In summary, respiratory failure in CMD begins with subtle changes in the quality and pattern of breathing in REM sleep, leading into under ventilation and low oxygen at night and eventually during the day. While early identification and treatment is not curative, it does reduce the burden on the affected individual and can improve quality of life.

Summary

1. Because there are no reliable clinical signs that reliably indicate the presence of chronic respiratory failure, caregivers and the medical team need to be acutely aware of the possibility of respiratory failure and then test for it appropriately.
2. Chronic respiratory failure can only be accurately diagnosed during a formal sleep study.
3. A home pulse oximetry study cannot be used to confirm the presence of or the absence of respiratory failure.

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Chronic Ventilation

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When to Screen for Chronic Respiratory Failure

Symptoms of sleep disordered breathing, of which respiratory failure is one component, include snoring, apneas, nocturnal sweating, morning headaches, poor concentration, daytime somnolence or an unexplained acceleration in weakness.[8] However, some affected individuals may be asymptomatic.[2,3,8,9] Although no single marker is an ideal predictor of SDB, the most commonly proposed is vital capacity (VC), which is a reassure of the total amount of air that an affected individual can breathe through the lungs with maximal effort. A VC of <40% is correlated with nocturnal hypoventilation or respiratory failure.[10-14] Maximal respiratory muscle pressures can also be predictive of respiratory failure. Maximal inspiratory pressures correlate better with respiratory failure than maximal expiratory pressures; however, both are less predictive than VC.[10,11,15]
It is important to use pulmonary function testing only as a component of a broader assessment of SDB since in affected individuals with CMD, and especially young affected individuals, it can be very challenging for them to produce reliable data. An alternate approach is to use the Sleep-Disordered Breathing in Neuromuscular Disease Questionnaire (SiNQ-5) [37] to screen for factors strongly correlated with SDB.

In SELENON (SELENON (SEPN1))-Related Myopathy, there is a poor correlation between skeletal and respiratory muscle weakness, and these affected individuals may present with early diaphragmatic weakness/failure even while they are still ambulatory.[16] So, early evaluation for respiratory failure is important.

How to Screen for Sleep Disordered Breathing

Please see the prior section on Assessment of Chronic Respiratory Failure for a description of the sleep study evaluation.

There are two important points to keep in mind:

1. Nocturnal pulse oximetry cannot be used to accurately assess for the presence of hypoventilation / respiratory failure. In other words, if performed, and it is normal, and without any desaturation, there can still be hypoventilation.
2. Independent of nocturnal hypoventilation, awake hypercarbia should be evaluated for at each clinic visit, either by end tidal or transcutaneous CO2 measurement.[18] A normal awake CO2 in no way insures the same measurement while the affected individual is asleep.

Starting Respiratory Support:

The long term benefits of respiratory support in Neuromuscular Disease have been well established; however, there is no benefit to early, “proactive” ventilation support before there is clear respiratory failure.

Initially, ventilation is provided by a non-invasive nasal interface, comfortably fitted to the affected individual's face and a ventilator set to support the affected individual properly. Perhaps the most critical part of NIV in affected individuals is the mask fitting - the most frequent cause of NIV intolerance is from an interface that the affected individual cannot tolerate.[19] Nasal interfaces come in two general categories: nasal masks that fit over the nose and nasal pillows that fit on or partially in the nostrils. An alternate interface that works well for some affected individuals is an oronasal (mouth and nose) or full face mask; however, there is a potential concern about stomach distention from air and an increased risk of vomiting into the mask. The ultimate choice is based on the affected individual's preference.

Minimizing leaks around the edge of the mask is a major challenge in acute and chronic NIV. Leaks are the result of inadequate fit between the skin and the mask or due to an open mouth. Leaks reduce alveolar ventilation and synchronization between the affected individual and the machine leading to suboptimal support.

Another other aspect of an adequate interface is the headgear. Headgear is needed to maintain the mask in optimal position. The majority of masks are designed specifically for NIV and used cloth straps with Velcro® to secure the mask. In infants or small children, finding headgear that fits a small head can be challenging. Custom modifications may be needed to provide a proper fit. In addition, for patients who have trouble keeping his/her mouth closed during sleep, a chin strap can be used to help keep the mouth closed and to optimize ventilation.

Non-invasive ventilation Settings

The most common type of chronic NIV uses pressure targeted modes (i.e. bi-level positive airway pressure or BiPAP). Single circuit pressured targeted ventilators provided with a calibrated leak, which is important because to allow for proper exhalation, a single circuit ventilator needs to have an exhalation port through which there is a continuous leak. These devices typically provide pressure-support ventilation (PSV), but can also provide pressure-controlled ventilation. PSV is achieved by setting inspiratory and expiratory positive airway pressures (IPAP and EPAP respectively) with the pressure support being the difference between IPAP and EPAP. A back-up rate can also be programmed to ensure the affected individual receives a minimum number of breaths.

The settings are titrated based on the individual. The main goal of NIV is to produce normal gas exchange and reduce the work of breathing. The IPAP and back-up rate are adjusted to deliver adequate ventilatory support and EPAP is adjusted to stabilize the upper airway (obstructive events). If EPAP needs to be increased, IPAP should also be increased to maintain an adequate level of PS (pressure support).[21,22] While this can be performed clinically, ideally the titration should be performed with continuous oxygen and carbon dioxide measurements. This can certainly be effectively performed in an inpatient hospital unit or during a polysomnogram as long as the paradigm used is to optimize ventilation (normal carbon dioxide) and oxygenation.

Besides setting inspiratory and expiratory pressures, most ventilators have other important parameters that can affect adequate ventilation.

Trigger: A common problem in affected individuals with neuromuscular disorders is their inability to trigger the ventilator to deliver and then stop a breath.[22,23] This is often a major challenge with affected individuals with respiratory muscle weakness and having a backup rate can insure that the

affected individual gets the necessary number of breaths.[24]

Rise time: the amount of time needed to reach the target pressure at the onset of inhalation. With a low rise time, it will take longer to reach the target pressure and vice versa. Rise time should be set to maximize the affected individual's comfort and minimize the work of breathing.[25]
***Ramp*:** This is a feature in the majority of newer devices. Ramp allows the pressure to increase gradually from a low level to the target level, thus improving affected individual comfort and adherence.[22-25] This could be a useful feature to help the affected individual adjust to the therapy.

***Cycle*:** This term refers to the change from the inspiratory phase to the expiratory phase. In general, most devices used for home NIV are cycled by time, thus a maximum inspiratory time is set. Leaks can affect cycling and the ability of a ventilator to sense a change in flow coming from the affected individual. Most new home ventilators have the advantage of allowing setting flow cycle criteria which could help to compensate for leaks.[22-25]

***Humidification*:** A common problem with NIV is nasal stuffiness and dryness of the nasal mucosa. This problem has been reported more frequently in affected individuals with nasal masks and mouth leaks.[26] Using heated humidification can decrease this discomfort,[27] and humidification level should be adjusted according to the affected individual's comfort. It is important to avoid excessive condensation in the circuit which could increase the risk of accidental aspiration. The risk can be limited by having the humidification set below the level of the affected individual's head or have a trap reservoir to capture the excess condensation.

NIV Modes

Bi-level positive airway pressure (BPAP) can be delivered in different modes. The spontaneous mode (S) in which there is no rate and only EPAP/IPAP, are set with the breath delivered on demand of the affected individual. This is usually not a recommended mode for affected individuals with neuromuscular weakness due to their inability to trigger a breath reliably. The spontaneous/time mode (S/T) where a rate is set in addition to an IPAP and EPAP and is the preferred mode of ventilation for affected individuals with neuromuscular disorders. The time mode (T), in this case a respiratory rate, is fixed and does not adjust based on the need of the affected individual.

Newer modes of NIV ventilation are now available. These modes are called "hybrid" modes since they combine features of pressure and volume ventilation. Newer devices used intelligent algorithms that automatically adjust the settings to achieve predefined targets.

Average Volume Assured Pressure Support (AVAPS): ventilation that guarantees a target volume (TV) with variable pressure support. In this mode, a target tidal volume (Vt) is set based on the affected individual's weight along with upper and lower limits of IPAP, EPAP and a back-up rate. The device will then auto adjust the IPAP pressures to target the desire Vt.[28-29]

Target volume with both variable pressure support and back up rate: besides automatically adjusting the PS to target a predefined TV, this mode of ventilation also adjusts the back-up rate (within a predefined range) to target a predetermined minute ventilation.[28-29]

***Target volume with variable pressure support, backup rate and auto adjusted EPAP*:** this mode combines the features of the prior mode but also auto adjusts the EPAP (with in predefine ranges) to

maintain airway patency. Additionally provides an automatic back-up rate to match the awake spontaneous affected individual respiratory rate.[28-29]

Table 5.1 Mechanical Ventilation Devices		
Goal	**Characteristic**	**Brand Examples**
Target volume with variable pressure support	Automatically adjust IPAP to reach a target TV	AVAPS (A40, Triology Phillips), Target volume pressure support (Vivo 50, Elysee 150 Resmed)
Target volume with both variable pressure support and back up rate	Automatically adjust IPAP and BUR to target minute ventilation	IVAPS (VPAP S9, Stellar 100, Astral Resmed)
Target volume with variable pressure support, back up rate and auto adjusted EPAP	Automatically adjust IPAP to achieve target TV, and EPAP level to maintain airway patency. Also provides automatic BUR to match affected individual respiratory rate	AVAPS AE (A40, Trilogy Phillips)

Mouth Piece Ventilation

Mouth piece ventilation (MPV), often called "sip and puff" ventilation, has been used since 1990. This a feasible option for affected individuals who are already on night time ventilatory support and have daytime respiratory failure. Some studies have shown MPV can reduce dyspnea and fatigue and improve speech and eating.[30] New ventilators with more sensitive triggers (i.e. kiss trigger in the Trilogy® 100) have design modes for mouth piece ventilation. The ventilator is usually set on assist control mode (AC) and a Vt is set up according to the affected individual's weight. Some of the disadvantages of MPV are air leaks around the mouth and nose. It also can cause gastric distension, increased oral secretion and on rare occasions vomiting. Failure of MPV is more often seen in uncooperative affected individuals and in affected individuals with severe bulbar (swallowing) muscle weakness.[30-32] An advantage of new ventilators is the option of setting more than one mode of ventilation, thus NIV can be set up for nighttime use and for mouth piece ventilation during the day.

Contraindications to NIV

There are a few contraindications for NIV, most of them are relative contraindications[33] with the final decision being left to the affected individual and their caregivers.

- Behavioral problems that could compromise adherence to therapy
- Skin lesions/trauma at the site of mask contact
- Inability to properly fit a non-invasive interface to the affected individual
- Both nocturnal and diurnal ventilation, though this is can be managed effectively if the affected individuals has multiple interfaces to alternate between
- Quality of life decision of the affected individual. Some affected individuals or families simply do not want a facial interface that obscures vision (affected individual) or view of the affected individual's face (family).

Tracheostomy

Use of noninvasive ventilation (NIV) has gained increasing popularity over invasive ventilation via tracheostomy to correct hypoventilation and sleep-disordered breathing in affected individuals with neuromuscular weakness in the last two decades.[34-36] Nonetheless, long-term mechanical ventilation via tracheotomy (IMV-T) remains a popular and frequent mode of respiratory support in cases of respiratory insufficiency or failure with ineffective NIV or when preferred by the affected individual.

Ineffective ventilation using NIV and an unstable upper airway, through which an affected individual cannot reliably breathe, are the only two absolute indications for invasive ventilation via tracheostomy tube.

While a tracheostomy tube can mitigate these issues, it adds the more important challenge of safely keeping the tracheostomy tube clear of secretions. This requires continual high-level nursing or a well-trained care provider.

Summary

1. Respiratory failure is the endpoint of any condition with progressive muscle weakness.
2. Early recognition is critical in minimizing the impact on an affected individual's function and quality of life.
3. There are a variety of different strategies for supporting ventilation and interfaces to deliver the ventilator support in a way that is best for the affected individual.

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Airway Clearance

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Introduction

Airway clearance is the mobilization and expulsion of airway mucus and the particles (bacteria, viruses, allergens, and irritants) that the mucus traps. It has two components: mucociliary clearance and cough clearance. In CMD, the primary problem is ineffective cough clearance.

The normal cough cycle is comprised of 1) stimulus, 2) inhalation, 3) glottic closure, 4) exhalation against a closed glottis to generate intrathoracic pressure, and 5) expulsive airflow as the glottis opens. The main muscles required for effective cough are the diaphragm, internal intercostals, and trachealis. Any weakening of these muscles results in impaired cough. Cough efficacy is tested objectively with peak cough flow (discussed in the Pulmonary Function Testing Section). Vital capacity and maximal inspiratory and expiratory pressures are also markers of cough efficacy. Impaired cough function can cause recurrent or prolonged lower respiratory tract infections. Importantly, subjective evaluation of cough (eg. cough "sounds strong or loud") is not an effective way to determine if there is an effective cough.

Most affected individuals with CMD have normal mucociliary function. However, some affected individuals with CMD develop bronchiectasis from chronic aspiration or recurrent pneumonia and atelectasis. Acute lower respiratory tract infections like pneumonia and bronchiolitis increase the quantity of airway secretions, and the secretions can become thicker and harder to clear.

Therapies

Cough Augmentation: The central component of assisted airway clearance in CMD is mechanically assisted insufflation-exsufflation. This supports maximal inhalation and exhalation. Serial inhalation to reach maximal inspiratory capacity (breath-stacking, glossopharyngeal breathing, or bag mask valve breaths) has been shown to stabilize vital capacity in affected individuals with Duchenne muscular dystrophy .[1] Achieving maximal inspiratory capacity can be followed by chest and abdominal thrust, which increases expiratory pressure and flow. Mechanical insufflation-exsufflation has largely replaced these manual maneuvers. Several devices are available (Cough Assist®, Philips Respironics, Carlsbad, California, USA and VitalCough®, Hill-Rom, Chicago, Illinois, USA). These devices provide cyclic positive inspiratory and negative expiratory pressures to allow a deeper inspiration and exhalation. A cough cycle can be triggered by the affected individual's inhalation automatically, based on setting a patient directed trigger, or manually by the care provider.

Proposed indications for initiation of mechanical insufflation-exsufflation therapy are FVC ≤ 50% predicted, MEP < 60 cm H_2O, or PCF < 270 LPM. Mechanical cough augmentation should be used routinely when well twice daily and more frequently during respiratory illnesses or after anesthesia. Frequency of use has not been well studied, but is really based on the need of the affected individual. Several institutions have clinical scoring tools that determine frequency of use during hospitalization, but these have not been validated or published.
The pressure settings are best determined by a trained therapist following the chest expansion of the affected individual, relative to the pressure applied during inspiration and exhalation, respectively. However, in a well-equipped pulmonary function testing laboratory it is possible to exactly measure volume of air inhaled relative to pressure applied. This of course is modified based on affected individual comfort and tolerance. Many affected individuals report barriers to daily use of these devices, including time commitment and social distractions.[2] Others report discomfort with optimal pressures due to chest stretch or abdominal inflation. Therefore, in order to achieve long-term adherence, some affected individuals may benefit from using sub-therapeutic pressures as an intermediate step to therapeutic settings.

Mucus Mobilization: Therefore, in select affected individuals, the addition of therapies targeted at mucus mobilization can be helpful. Limited data is available on the efficacy of mechanical cough and the addition of manual chest physiotherapy, high frequency chest wall oscillation (HFCWO), and intrapulmonary percussive ventilation (IPV) in CMD. HFCWO is safe and tolerated in children with neuromuscular disease[3] and may impact healthcare utilization in adults with amyotrophic lateral sclerosis.[4] IPV may be beneficial in affected individuals with Duchenne muscular dystrophy and tracheostomies[5] and is more effective than incentive spirometry.[6]

Using medications to make mucus less thick and easier to clear is not well studied in neuromuscular disorders. For thick or highly cellular mucus, potential mucolytic agents include inhaled normal saline, hypertonic (3% or 7% saline), and dornase alfa (deoxyribonuclease). These are not used routinely in affected individuals with CMD but can be considered during hospitalization for acute respiratory illness. Some affected individuals get better after using mucolytic agents such that they are prescribed on a routine basis. In the case of thin but copious secretions, agents that dry or reduce mucus production can be considered, but used cautiously to ensure that the secretions are not dried too much making them thick, adherent and hard to clear. Once again, the data supporting their use is limited in CMD.
Medications to decrease nasal or oral secretions, such as anticholinergic agents like gylcopyrrolate, scopolamine, and ipratropium, applied by enteral, transdermal, or inhaled delivery can reduce salivation. It is very important to be careful in titrating the doses so that lower respiratory secretions do not become too dry and difficult to mobilize. It is also important to consider gastroesophageal reflux as an etiology of increased oral secretions.

Mucociliary clearance can also be augmented with beta-adrenergic agonists. Albuterol increases ciliary beat frequency and has been proposed to improve mucus clearance.[7,8] Anticholinergic agents

(ipratropium) have been demonstrated to slow ciliary beat frequency and therefore may decrease mucociliary clearance and should be used cautiously.

Summary

1. Inadequate airway clearance is a challenge to recognize since it typically presents during an acute illness when effective airway clearance is really needed.
2. There are effective devices to both replace the cough (cough assist device) and other devices and medications that can be used to help move mucus more effectively with the cough assist device.
3. Taking a proactive approach in starting an airway clearance routine is critical in reducing the chance of severe respiratory difficulty during a cold, pneumonia or bronchitis.
4. It is absolutely critical to have an effective airway clearance regimen in place during an acute illness both at home and when in an emergency department or hospital inpatient unit.

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Acute Care

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Introduction

Acute care for children and adults with congenital muscular dystrophies (CMD) expands upon the vigilant respiratory and multidisciplinary care recommended for outpatient management. Providers and those affected, however, must recognize that CMD associated needs and risks are not uniform. Basic principles may be generalizable but should be customized to the specific needs of the affected individual based on his/her clinical symptoms and goals. Because of impaired airway clearance individuals affected by CMD are particularly vulnerable to acute respiratory decompensation from community-acquired infections or aspiration. Hospitalization may also be required during acute illnesses or changes in condition such as upper and lower respiratory tract illnesses, gastroenteritis with dehydration, bone fracture management, labor and delivery, and scheduled surgical procedures. Whether an admission is planned or unanticipated a great deal of planning and care coordination is required to insure a good clinical outcome.

The following recommendations are made based on case reports/series, reviews, prior guidelines for CMD and other neuromuscular conditions[1-3], and accepted clinical practice. When possible, recommendations were specified by CMD type, recognizing the clinical spectrum and that care should be tailored to the affected individual. The following grouped topics, accompanied by the associated published literature, represent priorities:

Assessment and Management Priorities

The following factors are critical in the successful management of the respiratory needs of an affected individual with CMD in order of importance:

1. Adequacy of airway clearance
2. Ventilatory status and potential need for increased support
3. Potential for secondary bacterial respiratory infection
4. Need to maintain nutritional status to avoid permanent loss of muscle function

In the early stages at home, it is critical for the family and other caregivers to recognize a change from normal and to proactively and aggressively manage it. In doing so, it is also important to have clear expectations about what level and intensity of care is and is not sustainable at home, and at what time additional care in the inpatient setting may be best. Clearly, high intensity respiratory care at home done 2-4 times a day routinely is not sustainable when needed more frequently.

Medical Transport Considerations and Emergency Department Evaluation

There needs to be a plan in place for safe transport to the closest medical facility that can treat and effectively manage the affected individual or stabilize for transport to a facility that can. Irrespective of the ultimate location, the following general recommendations need to be considered:

1. The individual or family should have a brief summary of medical needs, list of primary providers, and care protocols.
2. Presentation to the closest facility should be considered based upon the affected individual's degree of illness, distance from a tertiary facility, availability of pediatric or specialized transport team, environmental considerations, and goals of care.
3. Self-transportation can be considered during subacute events, assuming that respiratory support and monitoring provisions are available with one person driving and a second to care for the child/ adult. If there is not a second person to monitor the affected individual in the car, EMS should be used.
4. Distance from health care facility will also determine need for EMS
5. For affected individuals with CMD, emergent transportation should be provided via EMS with ACLS capacity and pediatric providers. If available a dedicated pediatric transport team is recommended.
6. The family should bring home equipment (e.g., BiPAP, ventilator, cough assist, mask interfaces, gastrostomy adaptors) for use during transport.
7. Those affected individuals who use noninvasive ventilation need a portable power supply for travel without use of emergency personnel: if that is not available, EMS should be used.
8. Large centers may not have protocols in their Emergency Department for acute management of affected individuals with CMD, or the front line clinician may not be familiar with the important aspects of management. If so, provide the contact information for the primary neuromuscular team.

Hospitalization (Community vs. Tertiary/Specialty Center)

1. Irrespective of an elective or acute hospitalization, children with CMD should be hospitalized at a hospital with expertise in the management of affected individuals with neuromuscular disease, including both cough assistance techniques and non-invasive and invasive ventilation.
2. Adults with CMD can consider hospitalization at a community hospital, but access to a consultant experienced in the management of affected individuals with CMD is critical. Any change in clinical status should prompt transfer to a center experienced in managing affected individuals with CMD.
3. The single most important factor initially is aggressive airway clearance with a cough assist device
4. Should there be trouble breathing initiating/maintaining ventilation must be done before there is any consideration for adding supplemental oxygen

Site of Inpatient Care (i.e., general ward, intermediate or specialty unit, ICU)

1. Triage depends upon CMD type, age, clinical status, goals of care, and institutional specific resources. All providers: RNs, MDs, RTs, PAs should be aware of nuances of respiratory assessment and management in CMD. The default should be to a higher level of monitoring and capacity for support (ICU) until the affected individual is stable and it is clear that their care can be managed effectively on a less acute medical unit.

2. Children and adults with CMD with stable ventilatory status and a low risk of developing acute respiratory failure can be managed on a general ward that is equipped to provide aggressive airway clearance.

Goals of Care / Resuscitation status

Be aware that offering respiratory and other medical support to affected individuals with CMD may be influenced by provider/institutional biases. The leader of the care team (on-service or outpatient physician) should set the plan for the limits of care, and if there are any after discussion with the affected individual and family. It is best to have a discussion prior to acute events and as part of pre-procedural planning, so that the affected individuals and families wishes for care can be honored through the entire hospitalization.

Engaging Primary Care and Primary Team (generalist and specialty providers)[4]

Individualized anticipatory care plans should be developed for outpatient family management and for escalation of care as needed during acute illness. This should include the signs and symptoms that should immediately prompt escalation of care. There should also be a clear plan to follow including cough assistance, other airway clearance, ventilation, nutrition, hydration, antibiotics, and emergency contact.

At the onset of increased respiratory symptoms, it is critical to communicate with the specialty care providers to help direct the care and determine at what point escalation and hospital management might be needed. This also should be done as part of discharge planning and transition of care back to the outpatient management team.

Pre-Procedural Management (anesthesia / sedation consideration [5, 6], and pain management)

1. Anesthesia and procedural sedation should be provided at tertiary care centers familiar with CMD, and with comprehensive respiratory support protocols.
2. Procedural monitoring should include capnography as well as oxygenation and standard vital signs.
3. Decisions about invasive or non-invasive ventilation should be made with the focus on the affected individual's medical stability during the procedure, after consulting with anesthesia, critical care, outpatient medical team, and the family and affected individual.
4. If invasive ventilation is to be used, during the procedure there needs to be a clear plan for weaning ventilation and successful extubation post-procedure that both acknowledges and manages the respiratory limitations of an affected individual with CMD
5. The ICU should be considered first for post-procedure care until respiratory stability is insured.

It is important to fully understand the affected individual's current ventilatory status and how close he or she may be to nocturnal respiratory failure and the need for mechanical ventilation. If it is not well established, polysomnography (sleep study) with both oxygenation and capnography is important. Pulmonary function such as forced vital capacity (FVC) and respiratory muscle function testing is not a reasonable surrogate for polysomnography to determine the presence or lack of respiratory failure.

Because of the challenges affected individuals with CMD may have in re-recruiting and maintaining lung volume after a procedure, introducing the affected individual to lung volume recruitment and airway

clearance therapies, even if there is not a clear need when well, can be helpful in insuring a smooth extubation and recovery.

Pre Procedural Cardiac Assessment is Recommended for Affected Individuals with CMD Subtypes with a Possibility for Myocardial Insufficiency or Proarrhythmic States [7]:

Difficult airway status should be considered based upon mandibular contractures, limited neck mobility, positioning restrictions and other factors. A low threshold for deferring elective / non-emergent sedation/anesthesia should be considered during intercurrent illness across all CMD types. Procedural sedation should include CO2 monitoring as the risk of hypoventilation is significant and may not be recognized with only oxygen saturation assessment or obscured by empiric utilization of oxygen supplementation.

CMD is not associated with malignant hyperthermia, as is the concern for central core / ryanodine receptor (RYR1) myopathy and Duchenne or Becker MD(15), thus standard anesthetic technique with inhaled agents can be considered; total intravenous anesthetic (TIVA) and "clean" techniques can also be provided(16). There is not enough evidence to make a clear recommendation about the use of depolarizing neuromuscular blockade (succinylcholine). Opiate-based analgesia should be considered as part of routine post-procedural pain management. Regional analgesia should be considered for all CMD types. Affected individuals with neuromuscular diseases are at increased risk for peri-procedural complications, including airway problems, suboptimal pain control (which has can certainly cause tachypnea, which can lead to inefficient ventilation), pulmonary complications, prolonged recovery times, and complications of bed rest and deconditioning.[17, 18]

Respiratory protocols[19-22] (Also reference Pulmonary/Respiratory Care Section)

1. The use of clear respiratory protocols in neuromuscular disorders has been shown to improve clinical outcomes.
2. Continued utilization of baseline supports (e.g., Cough Assist® / in-exsufflation and non-invasive ventilation (NIV)) are central to acute care management, independent of the process prompting hospitalization.
3. Cough assist, augmented secretion clearance, can be utilized effectively through the native or artificial airway. The pressures are typically between +30-40 cm H2O for insufflation and -30-40 cm H2O for exsufflation; however, the pressures should be titrated to effect by an experienced respiratory care provider.
4. Oxygen supplementation to address hypoxia should be utilized in conjunction with positive pressure, either NIV or invasive ventilation. It is generally accepted that extubation to NIV should be deferred until the affected individual has been successfully weaned to an FiO2 of 0.21, insuring adequate ventilation and perfusion matching.
5. Because of the underlying respiratory muscle weakness, invasive ventilation weaning protocols involving weaning to CPAP and off of ventilation before extubation to "condition" the respiratory muscles should never be used.
6. CPAP should not be used to support ventilation and is only effective in specific obstructive sleep apnea in the absence of respiratory failure.

Nutritional Care

1. Early fluid and nutrition support (either parenteral or enteral depending on the affected individual's status) is very important, recognizing that individuals with CMD may have low glycogen stores. Insufficient calories may make respiratory failure and muscle weakness worse.
2. Prolonged periods of fasting when an affected individual is developing or is in acute respiratory failure should be avoided and parenteral nutrition should be considered early in the course of acute respiratory failure

Discharge Considerations

Well in advance of when the affected individual has improved to the point where discharge is possible, discharge planning is needed to insure that the affected individual will either be able to resume the level of care they had prior to admission, or the level they will need temporarily or permanently after discharge. This can involve home nursing and obtaining new medical equipment, and most importantly, ensuring that the caregiver/family is properly trained in using it. Finally, it is critical to ensure that the outpatient management team understands what has occurred during the hospitalization and what changes there may be to chronic management.

Summary

1. Early identification of an acute respiratory illness and aggressive care early in the course of the illness is critical to effective and efficient management of an acute illness.
2. Having an action plan with the necessary equipment and protocols for using it (airway clearance and ventilator support) is necessary when in an acute care setting.
3. A similar action plan is necessary for management after anesthesia for minor procedures and or surgery.
4. A multidisciplinary approach is important in managing acute respiratory illnesses as an inpatient and transition back to the outpatient setting.

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Acknowledgements & Additional Resources

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Cure CMD is grateful for the tremendous voluntary contributions made by the authors of this guide and their ongoing dedication to improving pulmonary care for affected individuals with congenital muscular dystrophy. Pulmonary care is complicated and no clinician can be expected to understand every possible disease with respiratory complications, especially ultra-rare conditions. If your pulmonary care team is not familiar with the care standards in congenital muscular dystrophy, please encourage them to review this guide and reach out for additional consultation.

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If your pulmonary care team would like an email introduction to any of the CMD pulmonary experts who contributed to this pulmonary care guide, please reach out to us at **breathe@curecmd.org**.

Additional Resources

Cure CMD's mission to advance research toward treatments for CMD, and improve the lives of those living with CMD through engagement and support of our community.

Learn more about Congenital Muscular Dystrophy:
Web: curecmd.org
YouTube: youtube.com/curecmd

As our understanding of the natural history for each subtype evolves, this guide will be periodically updated.