The Respiratory Management of Patients With Duchenne Muscular Dystrophy: A DMD Care Considerations Working Group Specialty Article

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Summary. In 2001, the Muscular Dystrophy Community Assistance, Research and Education Amendments (MD-CARE Act) was enacted, which directed federal agencies to coordinate the development of treatments and cures for muscular dystrophy. As part of the mandate, the Centers for Disease Control and Prevention (CDC) initiated surveillance and educational activities, which included supporting development of care considerations for Duchenne muscular dystrophy (DMD) utilizing the RAND/UCLA Appropriateness Method (RAM). This document represents the consensus recommendations of the project’s 10-member Respiratory Panel and includes advice on necessary equipment, procedures and diagnostics; and a structured approach to the assessment and management of the respiratory complications of DMD via assessment of symptoms of hypoventilation and identification of specific thresholds of forced vital capacity, peak cough flow and maximum expiratory pressure. The document includes a set of Figures adaptable as “pocket guides” to aid clinicians. This article is an expansion of the respiratory component of the multi-specialty article originally appearing in Lancet Neurology, comprising respiratory recommendations from the CDC Care Considerations project. Pediatr Pulmonol.

INTRODUCTION

In 2001, the Muscular Dystrophy Community Assistance, Research and Education Amendments (MD-CARE Act) was enacted, which directed federal agencies to coordinate the development of treatments and cures for muscular dystrophy. As part of the mandate, the Centers for Disease Control and Prevention (CDC) initiated surveillance and educational activities, which included supporting development of care considerations for Duchenne muscular dystrophy (DMD).

Consensus statements regarding the respiratory management of patients with DMD have been previously published. However, this is the first consensus statement

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based on the Rand/UCLA Appropriateness Method (RAM). The participants and sponsors of this project recognized that there is a lack of randomized, controlled studies in this field, precluding development of evidence-based guidelines. The RAM methodology was designed for just such circumstances and aims to objectify the consensus process, through repeated anonymous query of an expert panel regarding the appropriateness and necessity of clinically relevant scenarios extracted from extensive review of the medical literature. The scenarios and the results from the RAM questionnaires were refined through telephone and in-person meetings of the panel members, optimizing the clinical relevancy of the consensus recommendations. This document was adapted from a two-part multi-specialty article originally published in Lancet Neurology.2,3 This respiratory specialty article includes expanded sections on respiratory recommendations and areas of controversy. The Figures in this document were specifically designed to aid clinicians and they can be used as “pocket guides” to the assessment and management of the respiratory complications of DMD.

METHODOLOGY

The CDC selected 84 national and international experts and organized them into multi-disciplinary panels representing the range of specialties involved in DMD care. The panels developed a comprehensive plan of patient care using the RAM. During this process, 1981 peer-review articles on assessments and interventions used in the treatment of DMD were analyzed, of which 489 were used to create 389 matrices representing 70,302 hypothetical clinical scenarios.

The respiratory panel consisted of 10 members from a wide geographic distribution, representing the disciplines of adult and pediatric pulmonology and critical care medicine, neurology, sleep medicine, rehabilitation medicine, and respiratory/physical therapy.

In the initial round, 36 respiratory matrices representing 606 hypothetical clinical scenarios were rated anonymously for appropriateness on an ordinal scale of 1–9. Median ratings for each clinical scenario were tabulated and analyzed according to RAM guidelines. During a series of in-person and telephone conferences, the panel discussed the results and edited the matrices for the second round of rating, which included 33 matrices comprising 269 clinical scenarios. Assessments and interventions deemed appropriate without disagreement (27 matrices representing 115 clinical scenarios) were further rated for necessity on a similar 1–9 scale. After three rounds of independent ratings, the expert panelists reviewed and interpreted the ratings to develop a clinically relevant consensus document. There were no disagreements among the panelists regarding the final recommendations.

The interventions deemed necessary and/or appropriate without disagreement by the panel describe an infrastructure for provision of optimal respiratory care to persons with DMD, described in this document. This document includes the expert panel’s recommendations on necessary equipment, procedures, tests, and diagnostic evaluations. It also provides a structured approach to the assessment and management of the respiratory complications of DMD, emphasizing the assessment of hypoventilation and the identification of specific thresholds of forced vital capacity (FVC), peak cough flow, and maximum expiratory pressure.

RESULTS AND PANEL RECOMMENDATIONS

Necessary Equipment, Procedures, and Diagnostics

Clinics caring for persons with DMD should have the capacity to perform and interpret the tests listed in Table 1. In order to perform these tests, the following equipment should be available in the inpatient and outpatient medical settings:

- Pulse oximeter.
- Capnograph.
- Spirometer.
- Manometer for measurement of maximum inspiratory and expiratory pressure levels.
- Peak flow meter for measurement of peak cough flow.
- Lip seal adapters for patients with weak buccal musculature, for use with spirometers, manometers, and peak flow meters.
- Mechanical insufflation–exsufflation device, such as the Cough Assist®.
- Volume recruitment/deep lung inflation devices, such as self-reinflating manual ventilation devices (e.g., Ambu® bag).
- Mechanical ventilators and bi-level devices capable of providing noninvasive and invasive positive pressure ventilation.
- A selection of noninvasive ventilation interfaces (including lip seal, nasal, and full face masks).
- Tracheostomy tubes.

<table>
<thead>
<tr>
<th>TABLE 1—Recommended Diagnostic Testing for Patients With Duchenne Muscular Dystrophy</th>
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<tbody>
<tr>
<td>Testing that should be available in the clinic</td>
</tr>
<tr>
<td>Pulse oximetry</td>
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<tr>
<td>Spirometry</td>
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<tr>
<td>Capnography</td>
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<tr>
<td>Peak cough flow</td>
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<tr>
<td>Maximum inspiratory and expiratory pressure levels</td>
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<tr>
<td>Arterial blood gas sampling and analysis</td>
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<tr>
<td>Testing that should be available by referral</td>
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<tr>
<td>Overnight pulse oximetry or simultaneous pulse oximetry and</td>
</tr>
<tr>
<td>capnography measured in the patient’s home during sleep</td>
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<td>Polysomnography</td>
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</tbody>
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Necessary Personnel

Patients with DMD who have respiratory complications should be cared for by physicians and respiratory/physical therapists who are skilled in the initiation and management of noninvasive respiratory aids, including noninvasive ventilation and associated interfaces, lung volume recruitment techniques, and manual and mechanically assisted cough (see the Recommendations for Assessment and Therapy Section). These personnel, techniques and equipment, including an infrastructure for patient and caregiver education, should be available in the clinic and hospital settings.

The home care of patients with DMD who have respiratory complications should include close involvement of respiratory/physical therapists familiar with the techniques and equipment outlined above. Sleep technicians performing polysomnograms on patients with DMD should be familiar with the patterns of sleep disordered breathing manifested by patients with neuromuscular weakness, and should be skilled in titration and adjustment of noninvasive ventilation pressure levels. The panel acknowledges the intimate association between respiratory, cardiac, and gastrointestinal considerations in patients with DMD. Thus, the care of persons with DMD should take place in multi-disciplinary clinics that include a pulmonologist or other physician with respiratory expertise, as well as a respiratory/physical therapist, cardiologist, gastroenterologist, and nutritionist.

Recommendations for Assessment and Therapy

Monitoring of respiratory status enables timely prevention and management of the respiratory complications of DMD. A structured, proactive approach to respiratory management that includes the use of assisted cough and nocturnal ventilation has been shown to prolong survival.4–6 Patients with DMD are at risk for respiratory complications as their conditions deteriorate due to progressive loss of respiratory muscle strength. These complications include impaired respiratory secretion clearance, atelectasis, and susceptibility to pulmonary infections due to ineffective cough, nocturnal hypoventilation, progressing to hypoventilation during wakefulness, and sleep disordered breathing.16–24 Guidelines for the respiratory management of DMD have already been published.2–6 Critical therapies include noninvasive ventilation,25–31 lung volume recruitment techniques,32–34 and manual and mechanically assisted cough.35–42

The schema, presented in Figures 1–3, outlines the way that assessments and interventions should be utilized in patients with DMD as their clinical course progresses. In the ambulatory stage of DMD, the initial assessment of pulmonary function (e.g., measurement of FVC at least annually) familiarizes the patient with respiratory testing and permits identification of each patient’s peak level of FVC. Most active respiratory management occurs after the patient becomes nonambulatory and pulmonary function declines. The pulmonary section of Figure 4 links recommended assessments and interventions to the various stages of disease and comprises a respiratory action plan that can be enacted as the patient progresses to increasing levels of disease severity. Particular attention to respiratory status is required around the time of planned surgery (see the Respiratory Considerations for Patients Undergoing Surgical Procedures Section).

Prevention and Treatment of Respiratory Infections

Immunization with 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for patients 2 years of age and older. Annual immunization with trivalent inactivated influenza vaccine (TIV) is indicated for patients 6 months of age and older. PPV23 and TIV are not live vaccines, so either can be administered to patients treated with glucocorticoids. Up-to-date, detailed information on immunization indications, contraindications, and schedules can be obtained from various sources, including the American Academy of Pediatrics (http://aapredbook.aappublications.org) and CDC (http://cdc.gov/flu). Access to the latest vaccine information is essential since recommendations can change quickly, as illustrated by the recent emergence of H1N1 influenza virus. Moreover, the development of new vaccines (e.g., the 13-valent conjugated pneumococcal vaccine) has the potential to affect recommendations regarding the use of current vaccines (e.g., the 23-valent pneumococcal vaccine).

In addition to the use of manually and mechanically assisted cough, antibiotic therapy is necessary if evidence of a lower respiratory tract infection is established by culture, and antibiotic therapy is recommended, regardless of culture results, if a patient’s Sp02 remains below 95% in room air. Supplemental oxygen therapy may impair central respiratory drive and exacerbate hypoxemia.31,35,43 Thus, supplemental oxygen therapy should be used with caution, as it can improve hypoxemia while masking the underlying cause, such as atelectasis, mucus plugging, or hypoventilation. When patients experience hypoxemia due to hypoventilation, retained respiratory secretions, and/or atelectasis, then manually and mechanically assisted cough and noninvasive ventilatory support should be used to maintain SpO2 ≥ 95% at all times; substitution by oxygen therapy alone is dangerous.6

Indications for hospitalization include the inability to maintain SpO2 at 95% or greater in room air despite maximal use of manually and mechanically assisted cough and noninvasive ventilation. When endotracheal
intubation is necessary, noninvasive ventilation can be used to facilitate extubation, even in patients with poor baseline pulmonary function. This approach will usually avert the need for chronic ventilation via tracheostomy.\textsuperscript{44,45}

**Respiratory Considerations for Patients Undergoing Surgical Procedures**

The panel endorsed the recommendations of the American College of Chest Physicians statement on the respiratory and related management of patients with DMD who undergo anesthesia or sedation.\textsuperscript{46} The exclusive use of a total intravenous anesthetic (TIVA) technique is strongly recommended due to the risk of malignant-hyperthermia-like reactions and rhabdomyolysis when patients with DMD are exposed to inhalational anesthetic agents.\textsuperscript{47,48} Depolarizing muscle relaxants like succinylcholine are absolutely contraindicated due to the risk of fatal reactions.\textsuperscript{47,48}

Interventions are aimed at providing adequate respiratory support during induction of, maintenance of, and recovery from procedural sedation or general anesthesia and at reducing the risk of postprocedure endotracheal extubation failure, postoperative atelectasis and/or pneumonia.\textsuperscript{46} These goals can be achieved by providing noninvasively assisted ventilation and assisted cough after surgery for patients with significant respiratory muscle weakness as indicated by sub-threshold preoperative pulmonary function test results. Preoperative training in,
and postoperative use of manual and assisted cough techniques are necessary for patients whose baseline peak cough flow is <270 lpm or whose baseline maximum expiratory pressure is <60 cm water (these threshold levels of peak cough flow and maximum expiratory pressure apply to older teenage and adult patients). Preoperative training in and postoperative use of non-invasive ventilation should be strongly considered for patients with baseline FVC <50% of predicted and is necessary for patients with FVC <30% of predicted. Incentive spirometry is not indicated due to potential lack of efficacy in patients with respiratory muscle weakness and the availability of preferred alternatives such as mechanical in/ex-sufflation.

After careful consideration of the risks and benefits, patients with significant respiratory muscle weakness may be eligible for surgery, albeit with increased risk, if they have become highly skilled preoperatively in the use of noninvasive ventilation and assisted cough.

**Controversies and Areas of Future Investigation**

The areas of controversy that follow illustrate that there is a paucity of prospective, randomized controlled studies in the areas of respiratory assessment and management of patients with DMD. For example, the values of pulmonary function and oxygen saturation and the polysomnography results identified in this document as thresholds for specific therapeutic interventions and the recommended frequency of patient assessment are primarily based on consensus opinion and observational clinical studies. Likewise, important details of therapy, including how to
Fig. 3. Respiratory interventions indicated in a patient who has DMD (adapted from Bushby et al.2,3).
optimize mechanical equipment settings, are largely unstudied. The consensus recommendations in this document do not preclude the important fact that additional studies are needed to define evidence-based, cost-effective management strategies for the respiratory care of patients with DMD.

Although they were not identified by the RAM methodology as areas of contention among the panel...
members, a number of the recommendations in this consensus document may be viewed as controversial. With regard to the importance of multi-disciplinary clinics, the unavailability of specific personnel, such as gastroenterologists with an interest in neuromuscular diseases, may make our recommendations impractical. In the diagnostics section of our document, we endorse measurement of FVC, MEP, and PCF. The equipment needed to measure these parameters is generally readily available, and advanced skills are not required to perform the testing. However, alternative measurements such as sniff inspiratory pressure, or use of the spirometer, rather than a peak flow meter, to determine peak cough flow, may have merit and require further study. Also, it is not known if there are threshold levels below which serial measurement of pulmonary function are no longer clinically useful; for example, after patients have begun using assisted cough devices, or after they have progressed to daytime use of assisted ventilation, there may be no clinical implications to continued deterioration in their pulmonary function test results. With regard to therapeutics, our recommendation regarding the initiation of antibiotic therapy in any patient with DMD who is experiencing a respiratory infection and SpO₂ below 95% is controversial, because such patients may have atelectasis rather than bacterial lower respiratory tract infection.

In addition to the areas identified above, a number of areas were identified as uncertain and/or controversial via the RAM methodology, with dispersion or polarization of opinion among the panel members. These include: the use of large tidal volumes or high-pressure span bi-level ventilation for all or most patients; the utility of chronic home use of mucus mobilizers, such as high-frequency chest wall oscillation or intrapulmonary percussive ventilation; the relative merits of polysomnography compared with overnight oximetry or oximetry/capnography; the use of bronchodilators to aid respiratory secretion mobilization; and the use of anticholinergics, mucolytics, or botulinum toxin for uncontrolled respiratory secretions. The best method of assisting ventilation— that is, whether to choose noninvasive ventilation or ventilation via tracheostomy—can be a contentious issue. Agreement, however, was strong among the panel members, all of whom favored non-invasive ventilation in almost all clinical situations, as outlined in Figure 3.

Finally, the prolonged survival of patients with DMD, which is due substantially to contemporary cardiopulmonary therapies, has had profound medical and psychosocial implications, affecting patients, their families, healthcare providers, health care delivery systems, and society. The implications of prolonged survival need to be explored through a multi-disciplinary approach involving the relevant stakeholders, with the goal that technological advances in cardiopulmonary management that prolong life will be accompanied by improvements in patient quality of life.

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REFERENCES