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▶ **To cite this version:**

Kathryn R. Wagner, Noah Lechtzin, Daniel P. Judge. Current treatment of adult duchenne muscular dystrophy. Biochimica et Biophysica Acta - Molecular Basis of Disease, 2007, 1772 (2), pp.229. 10.1016/j.bbadis.2006.06.009 . hal-00562721

HAL Id: hal-00562721
https://hal.science/hal-00562721

Submitted on 4 Feb 2011

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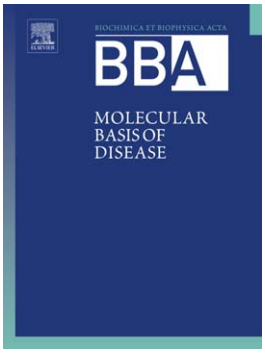

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PII: S0925-4439(06)00123-2
DOI: doi:10.1016/j.bbadis.2006.06.009
Reference: BBADIS 62603

To appear in: *BBA - Molecular Basis of Disease*

Received date: 5 May 2006
Revised date: 27 June 2006
Accepted date: 27 June 2006

Cite this article as: Kathryn R. Wagner, Noah Lechtzin, Daniel P. Judge, Current treatment of adult duchenne muscular dystrophy, *BBA - Molecular Basis of Disease* (2006), doi:10.1016/j.bbadis.2006.06.009

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Current Treatment of Adult Duchenne Muscular Dystrophy

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Abstract

Patients with Duchenne muscular dystrophy (DMD) are living longer into adulthood due to a variety of improvements in health care practices. This growing patient population presents new therapeutic challenges. In this article, we review the literature on current treatment of adult DMD as well as our own experience as a multidisciplinary team actively caring for 23 men ages 19 -38 years of age. Approximately one quarter of our adult DMD patients have remained on moderate dose corticosteroids. Daily stretching exercises are recommended, particularly of the distal upper extremities. Cardiomyopathy is anticipated, detected, and treated early with afterload reduction. Oxygen saturation monitoring, noninvasive positive pressure ventilation and cough assist devices are routinely used. Other medical issues such as osteoporosis, gastrointestinal and urinary symptoms are addressed. Current and future therapies directed at prolonging the lifespan of those with DMD will result in further increases in this adult population with special needs and concerns. These needs are best addressed in a multidisciplinary clinic.

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Duchenne muscular dystrophy (DMD) has long been considered a uniformly, fatal childhood disease. While there were few survivors of DMD beyond teenage years in the 1960s and 1970s, lifespan has been gradually extended in the past few decades [1]. With many DMD patients now living into their late 20s and 30s, it is now appropriate to anticipate that a current child with DMD will not only reach adulthood but may live well into his fourth decade. Improvement in survival with current treatments, and potentially enhanced by future therapies described in this issue, necessitates that physicians are informed regarding appropriate care for this emerging population. Although there is as yet scant data on outcomes, the consensus is that this care is best delivered by a multidisciplinary team. This article will review the literature and our experience caring for adults with DMD in a multidisciplinary clinic.

Patients with DMD are living longer into adulthood from a variety of factors. These likely include routine flu and pneumococcal vaccination, aggressive physical therapy and early use of antibiotics. Nocturnal ventilation has improved oxygenation, decreased atelectasis and has had a measurable effect on reducing morbidity and mortality [1]. Other changes in practice such as increased spinal surgery, use of afterload reduction for cardiomyopathy and earlier and prolonged use of corticosteroids are also likely contributors to increased survival, but there is currently insufficient data to evaluate their effects. Corticosteroid use has doubtlessly increased the number of years of ambulation. However, a correlation between walking and survival has not been demonstrated [2]. Perhaps one of the greatest contributors to increased survival for those with DMD is coordinated, multidisciplinary care.

Due to increasing numbers and specialized needs of adults with DMD, we have developed a multidisciplinary clinic dedicated to these patients. Patients were diagnosed by their pediatric neurologist by muscle biopsy showing lack of dystrophin immunostaining and/ or by

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genetic mutation analysis. Currently, there are 23 patients with a molecular diagnosis of DMD actively participating in our adult DMD clinic ranging in age from 18 to 38 (mean age 24). Nineteen of these patients are Caucasian, 3 African-American and 1 Asian-American. A seamless transition is made from pediatric specialists to adult specialists by concurrent clinics in the same Muscular Dystrophy Association (MDA) center where adult specialists are introduced to patients prior to assuming their care and where records are shared electronically. Patients and families are seen by a neurologist, pulmonologist, cardiologist, physical and occupational therapists, care coordinator and where appropriate, social worker and genetics counselor. Twice yearly visits are encouraged to keep abreast of changes in health status and to decrease the number of hospitalizations.

Neurologic Care

The neurologist acts as orchestrator of services and becomes, in many instances, the primary medical doctor. Although all adults with DMD should have identified a pulmonologist and cardiologist familiar with their disease, the neurologist coordinates the care of these specialists. For example, as discussed below, history taken by the neurologist on number of chest infections and signs of nocturnal hypoventilation is important in making a collective decision regarding cough and ventilation assist devices. Similarly, shortness of breath, peripheral edema and orthopnea are important considerations for discussion of afterload reduction with the cardiologist.

Corticosteroids: Glucocorticoid corticosteroids improve muscle strength and function in children with DMD treated from six months to two years as shown in randomized controlled clinical trials [3, 4]. The most effective dose appears to be 0.75 mg/ kg/ day [5]. Whether to continue corticosteroids as an adult, and at what dose, is a decision that the neurologist makes with the patient and family. The decision is difficult due to known systemic risks of long-term steroid use and unknown, but potential, benefits to respiratory and cardiac muscle. The 2006

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Cochrane review of corticosteroid use in DMD could not evaluate long term benefits from currently published studies [5]. While the conventional practice several years ago was to discontinue steroids when the patient began to use the wheelchair full time, many patients are continuing to use steroids indefinitely with the hopes that it provides benefit to muscles of respiration. There is some data to support respiratory benefit as measured by forced vital capacity; however, these trials were also in children and short term [3, 4].

In our adult DMD clinic, we do not initiate patients on steroids who have chosen not to take steroids or have discontinued them due to side effects or uncertainty of benefit. In adult patients who have chosen to continue on steroids after loss of ambulation, we assess the current side effects and if not overly burdensome, attempt to maintain steroids dosing. Although long-term steroid use has a host of well described side effects including weight gain, development of Cushingoid facies, short stature, hypertension, hyperglycemia, cataracts, and osteoporosis, by far the most common reason patients found to discontinue prednisone was excessive weight gain which inhibited transfers and care. Practice parameters developed by the Quality Standards Subcommittee of the American Academy of Neurology recommends decreasing prednisone to 0.5 mg/kg/day if weight gain >20% over estimated normal weight for height occurs over a 12-month period with further decrease to 0.3 mg/kg/day if excessive weight gain continues [6]. Six of our 23 adult DMD patients have continued on low to moderate dose prednisone but none have been able to tolerate and sustain the 0.75 mg/kg dose that they were originally treated with when ambulatory. The mean daily dose for those taking prednisone in our adult clinic is 0.33 mg/kg/ day, however, four of six have alternate day regimes. Similarly, Pandya et al., 2005, evaluated 30 patients for a 10 year follow up and found that prednisone dose was decreased to a mean dose of 0.36 mg/ kg/ day [7].

Exercise: Most adults with DMD have very limited motor abilities. However, some upper extremity muscles, especially finger flexors, may be well preserved and afford the patient the important abilities to control a motorized wheelchair joystick, play electronic games and use

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the computer keyboard. Physiotherapy should concentrate on stretching the upper extremity muscles to minimize contractures. A daily stretching routine should include elbow flexors, forearm pronators, wrist flexors, and long finger flexors [8]. Stretching of the lower extremities, (hip flexors, knee flexors and foot plantar flexors) should also continue past the period of ambulation and into adulthood as this provides relief from symptoms of stiffness and improves pain. In addition to stretching, patients benefit from therapy in the pool with assistance and support of the head and neck, where the buoyancy provides a degree of freedom of movement.

Cardiac management

As supportive care for individuals with DMD leads to greater longevity, both recognition and treatment of cardiac manifestations are increasingly important. Prior to the development of noninvasive methods to assess cardiac function, the incidence of myocardial dysfunction among those with DMD was thought to be low, but cardiomyopathy was often seen on autopsy [9]. Today, detection of asymptomatic left ventricular dysfunction and arrhythmia allows early and potentially life-saving treatment. In our practice, screening for anticipated cardiomyopathy is routine and co-incident with the diagnosis of DMD.

Incidence of dilated cardiomyopathy (DCM): In addition to its role in skeletal muscle, dystrophin plays an essential role in stabilizing the cytoskeletal complex within cardiac myocytes. Alterations in several components of this complex are associated with DCM (with or without associated skeletal myopathy), including delta-sarcoglycan, desmin, and metavinculin [10, 11, 12]. Despite consistent absence of dystrophin, however, the cardiac phenotype among DMD patients varies from no discernible left ventricular (LV) enlargement or dysfunction to early onset DCM with heart failure. The overall incidence of DCM in DMD has been estimated to be 25% by 6 years of age, 59% by 10 years of age [13]. By adulthood, nearly all people with DMD have cardiac involvement [13, 14]. As cardiomyopathy is an age-dependent disorder to which all DMD patients are genetically predisposed, there is a high likelihood of cardiac dysfunction over

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an affected individual's lifetime. Frequently, significant cardiac abnormalities predate symptoms [9, 13]. Accordingly, serial non-invasive assessment of cardiac dysfunction and early therapeutic intervention is strongly recommended.

Risk factors associated with the onset and severity of DCM are not clear. Severity of cardiomyopathy is not directly proportional to skeletal muscle strength, as has frequently been observed in Becker muscular dystrophy (BMD) patients who have nearly normal limb strength and receive cardiac transplantation for cardiomyopathy. Recently, there has been a suggestion that the deletion location may be linked to DCM. Jefferies and colleagues recently reported that in 47 individuals with DMD or BMD there was a higher incidence of DCM in those with a deletion occurring in exons encoding the N-terminal portion of dystrophin, and lower incidence of DCM in those with deletions occurring in exons encoding the C-terminus of dystrophin [15]. Data from additional subjects and follow-up of these initial individuals will be important to further evaluate this possibility, which could be an important tool in predicting cardiomyopathy.

Methods of detecting DCM: Scoliosis, positive-pressure ventilation, and flexion contractures may all contribute to difficulties in obtaining reliable data from cardiac imaging, and each of these factors should be taken into account when considering the best method of determining cardiac size and function. Options include echocardiography, magnetic resonance imaging (MRI), and multiple gated acquisition scan (MUGA). Additional methods, such as serum B-natriuretic peptide (BNP) or noninvasive impedance cardiography, may be useful, but at this point, there is not sufficient data to support their routine use in this population instead of more traditional techniques. Electrocardiography (ECG) is useful for determination of cardiac arrhythmia, but lacks both sensitivity and specificity in assessment of structural cardiac disease. A normal ECG does not provide adequate evidence of normal cardiac size or function, and an abnormal ECG provides no quantification of cardiac dysfunction (if present). In our practice, we perform ECGs when there is concern for arrhythmias such as atrial fibrillation, supraventricular tachycardia, or heart block (which is less common). We do not routinely perform surveillance

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ECGs for evidence of cardiac enlargement or dysfunction, as their yield is relatively low in comparison to echocardiography.

Echocardiography allows determination of the left ventricular (LV) size, wall thickness, valve function, as well as both LV systolic and diastolic function. While it may be technically limited in some patients with DMD, the use of intravenous echocardiographic contrast agents may improve its accuracy and feasibility. As opposed to some other methods of cardiac imaging, echocardiograms can be done while the patient remains in a wheelchair, which is a significant benefit to advanced patients with poor pulmonary function and hip contractures. While interpretation of the ejection fraction can vary among qualified readers, methods used to quantify cardiac performance may limit such variability [16]. In addition, factors such as intercurrent illness or respiratory insufficiency may be taken into account during interpretation of the study.

Cardiac MRI provides one of the most accurate assessments of LV size and function, and also adds the ability to image focal myocardial scarring. However, it is necessary to gate images such that data are not indiscriminately acquired throughout the cardiac cycle. Cine-MRI can be accomplished by compiling multiple images from evenly spaced phases of the cardiac cycle in a cinematic display. Limitations of cardiac MRI include the ease with which motion results in artifact, high cost, and technical factors related to acquisition of images in a narrow compartment for individuals with DMD.

MUGA scanning is performed by radiolabeling red blood cells, then measuring the activity of the radiotracer inside the cardiac chambers in systole and diastole through an external camera. It is one of the most accurate and reproducible methods of determining LV ejection fraction [17]. However, this method is limited in its ability to provide information about LV wall thickness or cardiac valve performance. As with cardiac MRI, limitations related to patient immobility may make this technique less desirable for some individuals.

The consensus statement from the 107th ENMC International Workshop recommends that DMD patients have an echocardiogram and ECG at diagnosis, every two years to age ten, and

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annually after age ten [18]. In our adult DMD practice we use echocardiograms yearly until cardiomyopathy is identified, and subsequently if there is a change in clinical status, such as worsening symptoms or arrhythmia, or if the results of the repeat echocardiogram are likely to change management. This practice is in accordance with published guidelines for all forms of dilated cardiomyopathy [19]. Although echocardiography may be less sensitive than MRI for determination of cardiac size and function, we find that it has significant advantages of cost and convenience for DMD patients. Our hope is that additional research will determine the role of advanced cardiac imaging techniques in this population.

Cardiac arrhythmia: Both bradycardic and tachycardic arrhythmias can occur in DMD. Sinus tachycardia is the most common cardiac arrhythmia associated with DMD. Possible mechanisms contributing to resting tachycardia seen among adults with DMD include profound deconditioning, adrenergic stimulation, or reactive increase in heart rate in response to poor cardiac function.

The risk of life-threatening ventricular arrhythmia is increased for patients with low ejection fraction, as has been noted for DCM of any cause [20]. Attempts to identify electrocardiographic indications of increased risk have also been performed. Among 84 individuals with DMD age 18.6 $\pm$ 4.8 years, Corrado and colleagues reported no additional prognostic value of standard or signal-averaged electrocardiography, or 24-hour Holter telemetry monitoring [21]. In contrast, QT dispersion is a marker of myocardial electrical instability, and when increased, is an indication of elevation in risk of ventricular arrhythmia [22]. Yotsukura and colleagues performed QT variability testing in 67 people with DMD, average age 20.5 $\pm$ 4.7 years, and showed that increased QT dispersion is a marker of ventricular arrhythmia in this population [23].

Implantable cardio-defibrillators (ICDs) are becoming more widely used for patients at highest risk of fatal or life-threatening ventricular arrhythmias. However, receipt of an ICD remains a very personal decision for those at risk of life-threatening ventricular arrhythmia.

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While many people with DMD meet the current standard in the United States of qualifying for an ICD on the basis of an ejection fraction less than 35%, published guidelines discourage use of ICDs for people with untreatable terminal illness or life-expectancy less than 6 months despite ICD placement [24]. Furthermore, use of standard medications described below can improve the ejection fraction and decrease the risk of ventricular arrhythmia.

Prior to consideration of an ICD, it is our practice to use medical therapy to both improve cardiac function and decrease risk of arrhythmia. If medications are not successful in improving the ejection fraction to greater than 35%, or if symptomatic ventricular arrhythmia (syncope or presyncope) occurs, then risks and benefits of ICD are considered and discussed in detail with the patient and family. This is a difficult topic for adolescents and young adults, though for those at greatest risk of life-threatening cardiac arrhythmia, it can be quite successful at prolonging life [25, 26]. The risks of psychological harm, inappropriate firing, and procedural complications of ICDs should be carefully considered in relation to the risk of sudden arrhythmic death for any patient considering an ICD. Of 23 adult DMD patients in our practice, one has received ICD and several are considering this therapy.

Treatments for cardiac complications: In the absence of large clinical trials with adult DMD patients who have DCM, medical therapy is derived from multiple large clinical trials which enrolled varied groups of patients, including ischemic, valvular, genetic, and acquired forms of DCM. In these populations, clear benefits have been demonstrated with several therapies regardless of the etiology of DCM, making it a reasonable extension to use these medications in a population affected with DMD. Smaller clinical trials noted below have assessed treatment for patients with DMD more specifically.

Use of angiotensin converting enzyme inhibitors (ACEi) is based on several large, well designed, prospective trials that show improved survival and decreased symptoms with this therapy for patients with DCM. The CONSENSUS-1 trial reported a 40% reduction in mortality at 6 months in patients with severe heart failure when treated with enalapril versus placebo, in

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addition to standard therapy [27]. Similarly, in a cohort of less symptomatic patients with DCM, the SOLVD trial showed 16% reduction in mortality with enalapril treatment compared to placebo [28]. The SAVE trial randomized patients with recent myocardial infarction and ejection fraction less than 40%, but notably without symptoms of heart failure, to receive either captopril or placebo [29]. During the follow-up period of 42 months, those treated with captopril had both improvement in survival and reduced morbidity and mortality due to major cardiovascular events.

As a class, ACEi are associated with side effects, including cough and angioedema. Because of this, studies testing the comparative benefits of angiotensin II-type 1 receptor blockers (ARBs) in DCM have been performed. ARBs appear to have lower incidence of side effects and similar effects on reduction in mortality as compared to ACEi [30, 31].

Duboc and colleagues recently reported their analysis of ACEi prior to onset of LV dysfunction in patients with DMD [32]. They enrolled 57 people age 9.5 to 13 years with DMD and normal cardiac function to receive an ACEi (perindopril) or placebo in a double-blinded fashion. After 3 years, all participants received open-label ACEi and were followed for 2 more years. After 3 years there was no difference in cardiac function in the 2 groups. However, after 5 years, there were 8 people with ejection fraction less than 45% in the placebo group compared to 1 person in the ACEi-treated group ($p = 0.02$). Based on these results, the study authors suggest starting all patients with DMD on ACEi as early as 9 years age. By the time an individual with DMD is seen in our adult DMD program, if not already started on ACEi or ARB by our pediatric collegues, it is our practice to do so even if cardiac function is normal or nearly normal.

Similar to ACEi and ARB, there are many studies supporting use of beta-adrenergic receptor blockers in people with symptomatic DCM regardless of the etiology [33, 34, 35, 36]. This class of medications provides not only anti-arrhythmic therapy, but also improves ejection fraction and adverse ventricular remodeling [37]. In our practice, use of beta-blockade is standard for those with symptomatic heart failure and is added after ACEi or ARB for individuals with persistent asymptomatic LV dysfunction (ejection fraction less than 40%).

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For DMD patients with symptomatic heart failure, several additional medications are likely to provide symptomatic benefit and perhaps improvement in survival. In such cases, use of medications such as spironolactone, loop diuretics, and digoxin should be considered. The use of warfarin anticoagulation has been studied in several trials of dilated cardiomyopathy, and to date, has only been shown to be of benefit in the setting of concomitant atrial fibrillation, recent anterior transmural myocardial infarction, or upon demonstration of an intracardiac thrombus [38, 39]. We do not empirically treat our DMD patients with warfarin in the absence of a clear indication for its use other than low ejection fraction.

Emerging cardiac therapy: Yasuda and colleagues recently reported work performed in a murine model of DMD, the *mdx* mouse [40]. In dystrophin-deficient cardiomyocytes, they showed reduced compliance and increased susceptibility to stretch-mediated calcium overload. Testing whether these abnormalities could be attributable to loss of membrane integrity, they treated dystrophin-deficient mice with poloxamer 188, a compound previously shown to insert into artificial lipid monolayers and repair damaged biological membranes [41]. Remarkably, functional deficits in dystrophin-deficient cardiomyocytes were repaired by intravenous infusion of poloxamer 188, suggesting that membrane stabilizing therapies may be an rational therapy for DMD based on molecular dissection of disease pathogenesis [40].

Future trials investigating emerging therapies for more common forms of dilated cardiomyopathy such as calcium sensitizers, passive cardiac restraint devices, and other neurohormonal modulators, may identify improved therapies for this condition. In addition, there is an urgent need for targeted clinical studies of both pathogenesis and therapy of cardiomyopathy in dystrophinopathy patients.

Pulmonary Management

The majority of individuals with DMD eventually die from complications of respiratory muscle weakness [42]. This includes progressive restrictive ventilatory defects, chronic

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hypoventilation, and pulmonary infections [43]. As most people with DMD begin to develop respiratory muscle weakness in the second decade of life, nearly all adults will have respiratory compromise. The following section will briefly review respiratory muscle involvement in DMD, the evaluation and treatment of neuromuscular respiratory complications.

The principal muscles for inspiration are the diaphragm and external intercostals. These are assisted by the accessory muscles of respiration, the sternocleidomastoid and scalenes [44]. While expiration during quiet breathing is a passive act, forced expiration and coughing require use of the expiratory muscles including the internal intercostals and the abdominal wall muscles. When inspiratory muscle weakness begins, patients are able to increase their respiratory frequency and maintain adequate ventilation. However, as weakness progresses patients hypoventilate which results in elevated arterial CO_2 and hypoxemia. Weakness of expiratory muscles results in decreased speech volume and more importantly, inability to cough forcefully enough to clear airway secretions. This places patients at increased risk of pneumonia.

Respiratory Evaluation: Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. After age 10 to 14, patients gradually begin to lose respiratory muscle function. Estimates of the rate of loss vary from 0.04 L/year to 0.74L/year or 2% to 39% predicted per year. The median loss in vital capacity is estimated to be 8.0% predicted per year [45, 46]. Because the loss of respiratory function is very gradual and patients have severe arm and leg weakness prior to respiratory muscle weakness, most patients have little shortness of breath and few respiratory complaints. Therefore clinicians need to perform routine respiratory evaluations in order to detect progressive respiratory muscle weakness and impending respiratory complications. The American Thoracic Society's consensus statement on DMD recommends evaluation by a respiratory specialist twice a year after wheelchair confinement, fall in Vital Capacity below 80%, or age 12 [42]. In our practice, frequency of pulmonary follow-up is highly variable. Patients who have stable respiratory issues

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may only need to be seen annually, while other patients may need to be seen multiple times in a year.

Evaluation should include a thorough history including questions regarding dyspnea, orthopnea, cough, difficulty with secretions, swallowing problems and sleep characteristics. Lying supine places the diaphragm at a mechanical disadvantage, and puts additional loads on the diaphragm from redistribution of blood into the pulmonary vasculature and shifting the abdominal contents against the diaphragm [47]. As a result, patients with DMD may note orthopnea or may complain of difficulty sleeping. Hypoventilation is often more pronounced at night and can result in nocturnal hypercapnia, elevation of the arterial partial pressure of carbon dioxide, which can cause morning headaches.

Objective measures of respiratory function are important for prognosis and timing respiratory interventions. There is some debate regarding the optimal tests for individuals with DMD but spirometry is the most standardized, best studied single test to obtain. Spirometry measures the forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1). The forced vital capacity is the volume of air expired from a full inspiration to a full exhalation. Other useful testing includes maximal inspiratory and expiratory mouth pressures, cough peak flow rates, arterial blood gas measurement, end tidal CO_2 (the measurement of exhaled carbon dioxide, which should approximate arterial CO_2), oxygen saturation, and polysomnography. Cough peak flow rates can be measured with a standard peak flow meter attached to a tight sealing face mask [43]. Flow rates below 160L/min are felt to place individuals at high risk for mucous plugging and respiratory insufficiency. Cough peak flows fall during acute illness and a cough peak flow of 270L/min can fall below 160 during an acute infection. Therefore, many recommend initiating a series of pulmonary interventions (see below) when cough peak flow rates reach 270 L/min [48]. Alveolar hypoventilation is defined by an elevated arterial CO2. The best measure is obtained from arterial puncture but this is painful and can be technically difficult in adults with DMD due to limb contractures. Therefore capnography, measurement of exhaled carbon dioxide,

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may be an attractive alternative in these patients, though its use has not been thoroughly evaluated in this patient population. Pulse oximetry is a simple method to assess oxygenation. DMD patients are at risk for mucous plugging and pneumonia, both of which can cause abrupt declines in oxygen saturation. It has been recommended that individuals with DMD and cough peak flow ≤270 L/min be equipped with an oximeter at home to monitor their oxygen saturation regularly. Hypoventilation, atelectasis, or mucous plugging can result in oxygen desaturation. Patients should be instructed to initiate assisted cough techniques and assisted ventilation if their oxygen saturation falls below 95% [48].

As noted above, hypoventilation is likely to occur while sleeping well before it occurs during wakefulness. This can occur simply from muscle weakness but may be complicated by central or obstructive sleep apnea. The recommendations for ordering sleep studies vary but the American Thoracic Society Consensus statement recommends yearly polysomnography [42]. However, overnight studies in a sleep laboratory can be challenging for DMD patients due to problems with positioning and mobility. In our practice, we consider polysomnography if there are symptoms of sleep disturbance that may be respiratory in origin and daytime values for CO_2, O_2 and FVC do not warrant ventilatory support If patients have daytime hypercapnia, oxygen desaturation or a sufficiently low forced vital capacity, we initiate non-invasive ventilation without a sleep study.

Another crucial element of the pulmonary evaluation of individuals with DMD is discussion of advanced directives and attitudes regarding long term mechanical ventilation. Patients should understand the natural progression of DMD and should have ample opportunity to explore and learn about the various treatment options available. To this end, it can be helpful for patients to speak to other patients who have undergone tracheostomy and learn from their experiences.

Respiratory Interventions/Treatments: Noninvasive positive pressure ventilators (NPPV) are devices that force air into the lungs via a mask or mouthpiece rather than an

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endotracheal tube or tracheostomy tube. The most common NPPV devices in use today are bilevel pressure cycled units in which separate inspiratory and expiratory pressures are set. The level of positive pressure support delivered to the patient is the difference between the inspiratory and expiratory pressure. Many patients with DMD have central sleep apnea and require NPPV machines that allow a respiratory rate to be set. As respiratory muscle weakness becomes more pronounced increasing levels of support are needed. Volume cycled ventilators, which are ventilators that deliver a preset tidal volume rather than a set pressure, may be able to provide more support than bilevel pressure cycled ventilators. Some practitioners favor these over bilevel pressure ventilators as respiratory muscle weakness progresses. Because nocturnal hypoventilation occurs before daytime hypoventilation, most patients initially use NPPV during the night and eventually shift toward daytime use as well. During daytime use, a mouthpiece can be a particularly convenient interface. Ventilators can be attached to wheelchairs and mouthpieces can be attached in place next to the patient's mouth. This allows patients to take breaths from the ventilator when needed but does not interfere with eating or speaking. The criteria to initiate ventilatory support are not well defined in DMD. One clear cut indication to initiate NPPV is evidence of hypercapnia or hypoxemia during sleep or wakefulness. Some advocate initiating NPPV when the cough peak flow falls below 270 L/min. While an optimal value of FVC indicating the need for NPPV has not been determined, most health care insurers in the United States reimburse NPPV units for restrictive ventilatory defects due to respiratory muscle weakness when the FVC falls below 50% predicted.

Though randomized trials of NPPV in DMD are lacking, there are observational studies showing benefits. Noninvasive ventilation has been shown to improve hypercarbia, hypoxemia [49, 50], survival [1], and quality of life [50], and may delay decline in lung function [51].

Some advocates of noninvasive approaches to respiratory care in DMD, such as discussed above, argue that no DMD patients ever require tracheostomy [52, 53] and that quality of life is better and complications are fewer when patients are managed noninvasively [54].

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Nevertheless, this view is not universally accepted. Some patients find it easier to eat, drink, and speak with a tracheostomy than with various oral and nasal interfaces. Furthermore, there is concern that once a patient requires 24 hours ventilatory support, noninvasive ventilation is not as secure as a permanent tracheostomy. However, there are also disadvantages to tracheostomy. It requires surgery and the risks of anesthesia which are increased in this population. It requires hospitalization and is painful during the perioperative period and many patients have more pulmonary secretions shortly after having a tracheostomy tube placed. One of the more difficult factors to invasive mechanical ventilation is it requires that a caregiver be present 24 hours per day. Nursing support is not well covered by most insurance plans in the United States and this places both financial and emotional strains on families.

Decreased mobility and weakened cough place DMD patients at increased risk of complications from pulmonary infections. While there is no data regarding vaccination in this patient population, it is prudent to recommend pneumoccocal vaccination every five years and annual influenza vaccination.

Another important pulmonary intervention is assisted coughing. While manually assisted coughing can be of help, mechanical insufflation-exsufflation has been proven to produce greater cough velocities. Mechanical insufflation-exsufflation, is also known as cough-assist™, or an in-exsufflator. It is a device that delivers a high positive pressure through a mask, mouthpiece, or tracheostomy, which inflates the lungs. Then, either manually or automatically it rapidly cycles to a negative pressure mode and sucks air from the lungs. This effectively simulates a natural cough and has been shown to generate high expiratory air flow. Studies have documented flows as high as 4.1 L/sec [55]. In order to prevent infections and mucous plugging, mechanical insufflation-exsufflation should be initiated when the cough peak flow falls below 270 L/min and should be used at least twice daily. Combining oxygen saturation monitoring, with NPPV and mechanical insufflation-exsufflation has been shown to reduce morbidity and mortality in DMD [48].

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In 23 adult DMD patients cared for in our multidisciplinary clinic, six (26%) of patients are unable to perform pulmonary function tests. In those who can perform spirometry, the mean vital capacity is 1.22 liters or 29% predicted. Ten (43%) of subjects currently use or have used noninvasive ventilation in the past and six (26%) of patients have tracheostomy tubes.

Respiratory care for patients with DMD has improved dramatically over the last fifteen years. As a result both quality of life and survival have increased markedly. Patients with DMD need to have regular evaluations by pulmonologists, and need to be cared for by a multidisciplinary team that is fully familiar with noninvasive monitoring, ventilation, and assisted cough techniques. In spite of improvements in care, there are controversies regarding optimal methods for ventilation. These include debates over volume cycled ventilators vs. bilevel pressure ventilators, timing of ventilation and under what circumstances tracheostomy should be recommended. Further research will be crucial to resolve these clinical dilemmas.

Other Medical Issues

Orthopedic concerns: Osteoporosis is a major problem in adults with DMD. This apparently occurs primarily from decreased weight bearing with loss of ambulation but may be accentuated by long term prednisone use. Fractures, particularly of the lower limbs, occur during routine daily care, including transfers, physical therapy and dressing and are estimated in one study to occur in as many as 30% of wheelchair-dependent DMD patients [56]. Wheelchair-dependent patients may have less exposure to sunlight and have low Vitamin D levels. For these reasons, we routinely treat all our adult patients, with daily calcium carbonate plus Vitamin D as well as weekly alendronate to decrease bone resorption.

Scoliosis affects most patients with DMD and contributes to respiratory function compromise, pain and deformity. The decision to have surgical fixation of the spine is usually made in early adolescence and adults rarely have the orthopedic or cardiopulmonary criteria to consider surgery. Sixty percent of our adults DMD patients (14 of 23) had scoliosis surgery in

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adolescence and there was no correlation between adult FVC in those that had received surgery (mean = 19% of predicted) and those that had not (mean = 22% of predicted). The emphasis in managing spinal deformity in adult patients is rather on proper seating. Proper wheelchair fitting and adjustments are critical to slow deformities, maintain mobility and enhance quality of life [8, 57].

Gastrointestinal and urinary concerns: Gastrointestinal symptoms may be under treated in this patient population. Nonambulatory DMD patients are more likely to suffer gastroesophageal reflux and esophagitis due to involvement of pharyngeal and hypopharyngeal musculature than healthy peers or ambulatory DMD patients [58]. Constipation due to lack of ambulation and smooth muscle hypomotility may decrease lung volumes and coughing force. It is important that the neurologist ask about these symptoms which in many cases, can be simply treated. Proton pump inhibitors are very effective in treating reflux with very rare side effects. Good hydration, balanced dietary intake, docusate sodium (stool softener) and senna (a promotility agent) are recommended to prevent severe constipation. On rare occasions, acute gastric dilation occurs with or without acidosis. This is a potentially life-threatening condition but, if recognized, responds well to prokinetic agents, nasogastric tube decompression of gastric contents and intravenous fluids.

Urinary symptoms are common in both children and adults with DMD [62]. Many have urinary urgency and some have difficulty with daytime and/or nocturnal continence. Urinary symptoms should be evaluated by urodynamics, bladder ultrasound and urine microscopic analysis and culture as appropriate. Many will be aided by the use of anticholinergics such as oxybutynin [62]. Alternatively, a penile sheath attached to a collection bag may be used for urgency or incontinence and may be convenient for those who are away from home for any length of time.

Social Issues

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A variety of social issues are becoming more apparent as the adult DMD population grows. These issues are at least as important as the physical ones described above and include the need for quality care, personal independence, educational and employment opportunities, meaningful relationships and sexual activity. The ability to find and obtain practical aids is often difficult [2] and can be aided by occupational therapists and care coordinators. A social worker is also an integral part of the multidisciplinary team. Social issue should be discussed with patients, solutions sought and potential side effects, such as depression, treated. Thirty percent of patients in our adult DMD clinic (7 of 23) are receiving treatment for depression with selective serotonin reuptake inhibitors (SSRIs). However, despite physical limitations, several studies demonstrate that adults with DMD perceive a high quality of life, one that is underestimated by health care professionals [59, 60, 61].

Conclusion

A variety of changes in multidisciplinary care have contributed to children with DMD surviving well into adulthood. This number of adults with DMD is likely to grow substantially from continued changes in practice such as early and prolonged use of steroids, nocturnal ventilation and ACE inhibitors. In addition, future therapies discussed in this issue including gene and cell based therapies, as well as efforts to increase muscle growth and regeneration, will not necessarily cure but attenuate the disease and further increase the number of DMD adults. The collective clinical experience caring for this population is still small, and data sparse. It will be important to learn from these young men as we care for them.

Acknowledgements: The authors wish to acknowledge Helen Posselt, Katie McGuire and the many young men and families with DMD for helpful discussions.

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