Current Concepts in the Management of Duchenne Muscular Dystrophy

Robert J. Rinaldi · Matthew P. Mayer ·
Michael R. Dichiaro

Published online: 13 March 2013
© Springer Science+Business Media New York 2013

Abstract The management of Duchenne muscular dystrophy (DMD) has seen dramatic change over the past two decades. Improvements in clinical monitoring of disease progression, management of cardiac and pulmonary complications, and nutritional intervention have all led to decreases in co-morbidity commonly associated with DMD, and, as a consequence, quality of life and life expectancy of individuals with DMD have both continued to improve. This review will update the reader on current trends and recent advances in the diagnosis, management, and treatment of DMD, with a focus on reviewing pertinent current literature.

Keywords Duchenne muscular dystrophy · Cardiac · Magnetic resonance imaging · Nutrition · Pulmonary · Glucocorticoids

Introduction

The past two decades have seen dramatic change in how clinicians diagnose and manage Duchenne muscular

dystrophy (DMD). DMD is the most common dystrophinopathy and is secondary to a complete absence of the dystrophin protein in the sarcolemmal membrane of skeletal and cardiac muscle. The gene encoding for dystrophin is located on the short arm of the X chromosome in the Xp21 region. Closely related to DMD is Becker muscular dystrophy (BMD) which is secondary to a decreased quantity or abnormal quality of dystrophin, typically secondary to in-frame mutation within Xp21. Though similar in phenotype, BMD has a much milder degree of severity and slower clinical course. Because DMD is a progressive disorder, most boys demonstrate a steady decline in general strength during their first decade of life and become wheelchair dependent by 10–12 years of age. During adolescence, progressive and profound loss of strength leads to a loss of independence in most self care activities, as well as a decline in respiratory function and in the majority of patients, cardiac function. Life expectancy is typically into the early twenties, with most individuals dying from respiratory or cardiac complications.

To date, the only active pharmacologic interventions proven beneficial for the treatment of the underlying dystrophic process have been the corticosteroids prednisolone and deflazacort. Both medications have been shown in clinical trials to lead to modest improvements in muscle strength and function though duration of these benefits is typically less than 2 years. Despite their presently being no active cure for the underlying dystrophic process, marked advances in our understanding of the pathology behind DMD and resultant improvements in the care of cardiac, respiratory, and general health co-morbidities has led to significant improvements in the overall health, life expectancy, and perhaps, most importantly, the quality of life for these boys.

R. J. Rinaldi (✉) · M. P. Mayer
Section of Pediatric Rehabilitation Medicine,
The Children's Mercy Hospitals and Clinics,
2401 Gillham Road, Kansas City, MO 64108, USA
e-mail: rrinaldi@cmh.edu

M. P. Mayer
e-mail: mpmayer@cmh.edu

M. R. Dichiaro
Department of Pediatric Rehabilitation Medicine,
Children's Hospital Colorado, 13123 E. 16th Street,
Aurora, CO 80045-7106, USA
e-mail: Mike.Dichiaro@childrenscolorado.org

Diagnostic Imaging

Muscle MRI

After more than 20 years, the promise of magnetic resonance imaging (MRI) to impact clinical care and research for patients with DMD is nearing a tipping-point. At present, few patients with DMD are ever evaluated by MRI, but this fact is changing. Advances in MRI technology continue to make scans faster and more powerful with some muscle protocols now taking fewer than 5 min [1]. There is an increasing trend for MRI use in evaluation of skeletal and cardiac muscle for patients with DMD in clinical practice and research [2, 3].

The MRI may be clinically helpful at identifying patterns of muscle involvement, to guide the differential diagnosis for genetic testing, and to aide in tissue selection for biopsy [4, 5]. In evaluation of DMD, however, the diagnosis is typically made by history and physical exam, and then confirmed by genetic testing with invasive muscle biopsy many times being unnecessary. Although muscle MRI rarely aids the diagnosis of DMD, a recent study by Fischmann et al. [6•] suggests that MRI may be able to predict the natural course of the disease including estimating the time to loss of ambulation.

Fischmann et al., evaluated twenty patients with DMD using a quantitative MRI technique and found a high correlation in MRI data to clinical measures predicting loss of ambulation. Specifically, an MRI technique known as the 2-point Dixon method is used to calculate the fat fraction in major muscle groups of the thigh. The fat fraction data is then compared to the motor function measure (MFM), a clinical measure previously shown to have a predictive power of 1 year for loss of ambulation in DMD [7]. Fischmann et al., calculated an average increase in muscular fat of 5 % per year for patients with DMD. Using their proposed cutoff value of 50 % fat fraction for loss of ambulation, the important clinical and research implications of this study are highlighted by the objectivity of MRI data. While clinical measures such as the MFM are observer dependent and rely on full participation of the child, quantitative MRI protocols offer highly reproducible data which in this study were noted to be obtainable in 15–20 min with an almost universally available MRI technique. This pilot study supports MRI as a predictive tool for individual rates of disease progression with meaningful implications for family planning as well as outcomes during therapeutic trials.

As a research tool, muscle MRI may offer several additional advantages over functional measures. Specifically, muscle MRI may be more sensitive to change in early disease progression for patients with DMD. A recent case control study by Arpan et al. [8] looks at 30 patients

with DMD using proton transverse relaxation time (T2) MRI mapping of the lower leg. Findings included statistically significant T2 values compared to controls for patients 5 years of age and older as well as strong functional correlation across all age groups. Similarly, MRI may be more sensitive to change in late disease progression as further evidenced by another case–control study by Torriani et al. [9] which utilizes spectroscopy to correlate lower leg adiposity and functional measures for nine patients with DMD.

Muscle MRI also continues to challenge our basic science understanding of the pathophysiologic processes in DMD. A prospective case series by Weber et al. [10] uses a fat suppression technique of short T1 recovery (STIR) to look at sodium overload and muscle edema as a contributing cause for progressive muscle degeneration in DMD. Findings suggest that edema precedes fatty infiltration of muscle. Furthermore, edema is assessed as intracellular suggesting a mechanism for osmotic injury rather than edema related to inflammation. After MRI comparison of steroid-treated and untreated patients with DMD, the authors theorize that the muscle strengthening benefits of glucocorticoids such as prednisone are due to the anti-edematous effects of the medication. Advancing this notion, the authors share a case report of a 22 year old female with DMD who demonstrates decreased edema on MRI and markedly improved strength after treatment with eplerenone [10, 11]. If true, aldosterone antagonists could be considered as therapeutic alternatives with fewer side effects than glucocorticoids.

Cardiac MRI

The accuracy of echocardiography, the gold-standard for cardiac imaging in DMD, is limited by typical body habitus of patients including barrel-chests, obesity and scoliosis. The positive trend in MRI technology is advancing the use of cardiac MRI as a first-line test for patients with non-ischemic cardiomyopathies such as in DMD [12]. As expected, software and hardware improvements continue to reduce MRI scan times and improve image quality. A recent review article by Otto et al., outlines image capture techniques and cardiac function metrics such as strain and late gadolinium enhancement used to diagnose cardiac disease earlier and with greater sensitivity to change in patients with DMD [2].

Management of cardiac disease is increasingly important given the trend for improvements in life expectancy for patients with DMD [13, 14]. The asymptomatic patient with advanced cardiac disease and the patient with vague, non-specific symptoms present significant clinical challenges in the management of DMD. For researchers, MRI will play an important role in evaluating the effectiveness

of novel therapies to benefit the health of both skeletal and cardiac muscle.

Medical Management

Nutritional Status

Given the high incidence of obesity, the metabolic effects of chronic steroid use, and the dynamic decline in functional ability experienced by patients, the nutritional management of boys with DMD can be highly complex. Despite this, there is very little evidence or consensus in the literature guiding the development of appropriate nutritional strategies for boys with DMD [15••]. Two important issues that are frequently discussed in the clinical setting are the use of nutritional supplements to bolster strength and function, and the consideration of gastrostomy tube placement to allow for safe enteric feeding with reduced risk of aspiration.

The utilization of dietary supplements as an alternative medical treatment has garnered much attention by the public over the past decade. Perhaps the most studied supplements in the DMD population are creatine monohydrate and glutamine. The evidence supporting the use of creatine has historically been conflicting. A recent Cochrane review assessing randomized and quasi-randomized controlled trials of creatine use versus placebo in patients with dystrophinopathies suggests that short and medium-term use of creatine has a positive effect on muscle strength, functional testing, and subjective assessments of activities of daily living. Most studies demonstrated no significant side effects of its use when compared to placebo [16].

Glutamine has shown little benefit towards improving strength, muscle mass, or function in limited human studies despite evidence of it slowing down whole-body protein degradation [17–19].

Undernutrition and dysphagia occur commonly in DMD, especially as patients age into adolescence. Oropharyngeal dysphagia can result from a number of factors, including weakness of the oropharyngeal musculature, difficulties chewing, malocclusion, and macroglossia [20]. Dysphagia, combined with functional deficits in upper extremity strength, can make the facilitation of safe and efficient intake of enteric nutrition quite challenging in the older DMD patient. The efficacy and safety of gastrostomy feeding tubes for the administration of nutrition has been studied in the general neuromuscular population, but has received limited research attention in the DMD population specifically. Martigne et al. [21] recently demonstrated significant improvements in general nutritional status using weight to age ratio as their outcome in a population of 25

boys with DMD after placement of gastrostomy feeding tubes. However, post operative complications occurred in 84 % of subjects, with the majority (56 %) occurring greater than 1 month after the surgery. These efficacy results have since been supported with data from Mizuno et al. [22] and Diamanti [23]. Interestingly, Mizuno reported a postoperative complication rate of only 42 %, though this study was performed across many neuromuscular diagnoses and not just DMD alone. Regardless, the current data supports the use of gastrostomy tubes as a means of providing safe and effective enteral nutrition in the older DMD.

A primary concern regarding placement of a gastrostomy tube relates to the timing of surgery placement. Strong consideration of timing must be made based on the respiratory status of the patient, in conjunction with the severity of dysphagia and weight loss progression. Though no studies have specifically addressed this in DMD, studies in the amyotrophic lateral sclerosis (ALS) population suggest that postoperative complications can be minimized if gastrostomy tubes are placed when the forced vital capacity is >50 % of predicted values [24]. It seems intuitive to extrapolate this data to the DMD population when considering placement of a gastrostomy tube.

Respiratory Management

Individuals with DMD develop progressive weakness of the respiratory muscles with subsequent development of restrictive pulmonary disease in the first decade of life, resulting in progressive respiratory insufficiency. This can lead to significant respiratory compromise affecting quality of life and life expectancy. Current management strategies for the pulmonary compromise and complications associated with DMD typically include management of airway secretions and clearance via mechanical means, respiratory muscle strengthening and training programs, and non-invasive as well as invasive assisted ventilation. There is a paucity of controlled trial data in the literature to definitively support specific interventions over others within these domains. Despite this, consensus statement guidelines providing in-depth recommendations for the comprehensive respiratory management of patients with DMD have been published by the American Thoracic Society [25]. These guidelines are based on critical review of the available literature at the time of their publication and can serve as a good general guideline for the effective management of this population.

It has been well established that the use of non-invasive and invasive ventilator support has dramatically prolonged the life expectancy in DMD. Attention has more recently been focused on the efficacy of pharmacologic interventions to improve respiratory status. Because of the ubiquitous

nature of corticosteroid use in DMD, multiple studies have been done assessing their effect on pulmonary status. Balaban et al., demonstrated improvements in forced vital capacity (FVC) occurring over the ages of 7–10 years in boys treated with either prednisone (0.75 mg/kg/day) or deflazacort (0.9 mg/kg/day) [26]. However, between the ages of 10 and 15 years, those boys treated with deflazacort showed a continued trend of slight improvement in FVC while those boys treated with prednisone showed stabilization of their FVC. Likewise, in a retrospective review study, Biggar et al. [27] demonstrated efficacy of deflazacort (0.9 mg/kg/day) in improving FVC-percent predicted in boys between the ages of 10 and 15 years. More recently, Daftary et al. [28] demonstrated in a case controlled retrospective review an improvement in peak cough flow and respiratory muscle strength in boys with DMD who were treated long-term with prednisone. Despite the limitations of these studies (small sample sizes; retrospective design) they do suggest statistically significant beneficial effect of both corticosteroids on pulmonary function, with deflazacort perhaps having greater benefit in adolescence. For these reasons it has been this author's practice to continue steroid treatment in boys well beyond loss of ambulation if they tolerate potential side effects.

In addition to steroids, Idebenone, an inhibitor of lipid peroxidation and a potent antioxidant, has been investigated for potential effect on pulmonary function in the DMD population. It has previously been shown that idebenone has cardioprotective effects and improves exercise performance in the mdx mouse model [29]. A recent randomized controlled study demonstrated a beneficial effect of 12 months idebenone treatment on peak expiratory flow in boys 8–16 years of age, with effects more pronounced in a steroid-naïve study subgroup compared to a subgroup of boys concomitantly receiving steroids [30]. Though studies addressing the benefits of steroids and other medications on pulmonary function are limited, those results available are certainly provocative enough to warrant more in-depth investigation into their benefits.

Cardiac Management

Cardiac involvement in DMD has long been recognized, with cardiomyopathy being the second leading cause of death in this population. The incidence of cardiomyopathy in DMD increases with age, affecting 30 % of patients by 14 years of age, 50 % of patients by 18 years of age, and up to 90 % of older patients [31]. Given advances in non-invasive and invasive ventilator support leading to prolonged survival in DMD, the effective management of cardiomyopathy has become more crucial. Over the past 10 years, a growing body of evidence has emerged demonstrating a beneficial effect of pharmacologic intervention

on cardiac function in DMD. In a 2008 historical cohort study, Markham et al. [32] demonstrated that corticosteroids started prior to ventricular dysfunction provide a beneficial effect on both load-dependent and load-independent measures of cardiac function. However, to date no prospective randomized controlled studies have been done to verify this initial data or the benefits that steroids may impart upon cardiac function. The effects of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and angiotensin receptor blockers (ARB) on cardiac function in DMD have received considerable research effort over the past decade, with evidence showing beneficial effects on cardiac function preservation [33]. Subsequently their use has become commonplace in the management of DMD. However, one issue that has remained in question is if combination therapy has greater benefit than mono-therapy. In 2006, Kajimoto et al. [34] demonstrated beneficial effects of combination beta-blocker/ACEI treatment on ventricular function compared with ACEI treatment only. A follow-up study in 2012 by Viollet et al. [35] failed to show a significant difference between combination and mono-therapy, however. In addition, the timing of initiation of therapy remains in question, with no present evidence in the literature to suggest optimal ages or clinical stages at which cardiac medications should be initiated. Further research into these issues is clearly warranted if the full benefit of these medications is to be realized.

Treatment

Corticosteroids have been the only pharmacologic treatment shown to effectively treat and slow the progression of DMD. There are several other approaches to treatments for DMD, and significant research has been conducted in the last year on many of these methods. Several of the mechanisms under investigation include exon skipping by stop codon suppression, oligonucleotides that alter mRNA splicing for exon skipping, mini-dystrophin gene transfer with adeno-associated virus, myostatin inhibition, utrophin up-regulation, aminoglycosides for suppression of premature stop codons, phosphodiesterase inhibition, several mechanisms inhibiting inflammation, complementary and alternative treatments, etc. Below are also highlighted several studies from the many categories of treatment approaches.

Corticosteroids

There has been significant discussion about the most appropriate timing for initiating the use of corticosteroid treatment. The DMD Care Considerations Working Group's clinical care recommendations suggest the timing of initiation of steroids is an individual decision, but that starting

while the child is continuing to make motor gains, especially before the age of 2, was not recommended. Discussion of treatment between ages 4 and 6 was recommended when motor gains are often reaching a plateau [36]. Merlini et al., reported findings from an open, parallel study of boys with DMD treated with an alternate day treatment with corticosteroids, beginning between 2 and 4 years of age. Five boys were in the treatment group, and three in the control group. Of the five boys in the treated arm, one lost ambulation at age 10 and was lost to follow up. After 14 years of follow up, the remaining four were ambulatory at ages 17.0–18.5 years, three were able to ascend stairs and two were able to rise from the floor. All experienced growth retardation, decreased bone mineral density and delayed puberty [37••]. This argues for the benefit of early initiation of corticosteroid treatment, and for the importance of long term studies to investigate the timing of initiation (in addition to the specific steroid used for treatment and dosing regimen).

Exon Skipping: Ataluren (PTC-124)

Ataluren is a compound that induces ribosomal read through of stop codons in exon 51. This compound is under consideration by the FDA for treatment of boys with DMD.

Splice Switching Oligonucleotides: AVI-4658 (Eteplirsen)

Splice switching oligonucleotides are molecules that transform out of frame mutations at the mRNA level to in-frame mutations, similar to those found in Becker Muscular Dystrophy. The AVI-4658 is a morpholino splice switching oligonucleotide that had been shown in 2009 to induce exon 51 skipping and dystrophin production in a small study of IM injections in the extensor digitorum brevis in seven patients. [38]. In 2012, Cirak et al., demonstrated that along with dystrophin expression in the high dose injection group, AVI-4658 also shows significantly elevated expression of alpha-sarcoglycan in those with deletion in exons 45–50, significantly elevated expression of beta-dystroglycan in those with deletions of exons 45–50 and 48–50, and significantly elevated expression of neuronal nitric oxide synthase (nNOS) in those with deletions of exons 48–50. These are all important parts of the subcomplexes of the dystrophin-associated glycoprotein complex and are an indication that the truncated dystrophin protein produced is functional [39].

Phosphodiesterase Inhibitor: Sildenafil

Sildenafil is a c-GMP specific phosphodiesterase type 5 inhibitor that amplifies the nitric oxide-cGMP signaling pathways, increasing nitric oxide signaling which regulates

vasculature, muscle mass and fiber type and atrophy. In dystrophin deficient muscle, this signaling pathway cannot normally locate to the sarcolemma with the dystrophin-associated glycoprotein complex. Percival et al., administered Sildenafil orally to MDX rats for 14 weeks. Diaphragm muscle tested in vitro was found to have significant increase in force produced (~15 %) and reduction in TNF-alpha and fibrosis compared to the control MDX group. There was no significant difference in fatigue. Interestingly, Sildenafil did not improve hind limb strength, and appears to be muscle specific [40].

Anti-Inflammatory, Utrophin Up-Regulation: Resveratrol

Inflammation is thought to be an important component of the damage that occurs in dystrophic muscles. Resveratrol acts through the Sirt1 pathway, is an anti-inflammatory and up-regulates utrophin. Gordon, et al., demonstrated in MDX mice that administration of 100 mg/kg daily of resveratrol had the greatest increase in Sirt1 gene expression and reduction in cell inflammation found on immunohistochemistry. This dose also had significantly increased utrophin gene and protein expression in the tibialis anterior muscle with gene expression increased by 43 % compared to control MDX mice [41].

Complementary and Alternative Treatments

Data from the MD STARnet were reviewed to determine frequency and types of use of complementary and alternative medical treatments and showed that 80 % of caregivers reported using complementary and alternative treatments at least once [42].

Conclusion

Significant strides have been made in the comprehensive management of patients with DMD. With these gains have come decreases in the severity of associated co-morbidities, enhanced general health and quality of life, and prolonged life expectancy. Despite these changes, many questions and challenges still remain with respect to how our improved knowledge can be better applied. Further research in all areas of DMD management is warranted so that even further gains can be made in the care of individuals with DMD.

Disclosure RJ Rinaldi declares no conflicts of interest; MP Mayer's institution has received research grants from Allergan and MR Dichiaro declares no conflicts of interest.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Gaeta M, Messina S, Mileto A, et al. Muscle fat-fraction and mapping in Duchenne muscular dystrophy: evaluation of disease distribution and correlation with clinical assessments. Preliminary experience. *Skeletal Radiol*. 2012;41(8):955–61.
2. Finanger EL, Russman B, Forbes SC, et al. Use of skeletal muscle MRI in diagnosis and monitoring disease progression in Duchenne muscular dystrophy. *Phys Med Rehabil Clin N Am*. 2012; 23(1):1–10.
3. Otto RK, Ferguson MR, Friedman SD. Cardiac MRI in muscular dystrophy: an overview and future directions. *Phys Med Rehabil Clin N Am*. 2012;23(1):123–32.
4. Mercuri E, Pichiechio A, Allsop J, Messina S, Pane M, Muntoni F. Muscle MRI in inherited neuromuscular disorders: past, present, and future. *J Magn Reson Imaging*. 2007;25(2):433–40.
5. Costa AF, Di Primio GA, Schweitzer ME. Magnetic resonance imaging of muscle disease: a pattern-based approach. *Muscle Nerve*. 2012;46(4):465–81.
6. • Fischmann A, Hafner P, Gloor M, et al. Quantitative MRI and loss of free ambulation in Duchenne muscular dystrophy. *J Neurol*. 2012. doi:10.1007/s00415-012-6733-x *This study tests MRI as an objective measure to anticipate functional decline and loss of ambulation. Predictive tools such as this provide important information for patients, families and clinical trials.*
7. Vuillerot C, Girardot F, Payan C, et al. Monitoring changes and predicting loss of ambulation in Duchenne muscular dystrophy with the Motor Function Measure. *Dev Med Child Neurol*. 2010;52(1):60–5.
8. Arpan I, Forbes SC, Lott DJ, et al. T(2) mapping provides multiple approaches for the characterization of muscle involvement in neuromuscular diseases: a cross-sectional study of lower leg muscles in 5-15-year-old boys with Duchenne muscular dystrophy. *NMR Biomed*. 2012. doi:10.1002/nbm2851
9. Torriani M, Townsend E, Thomas BJ, et al. Lower leg muscle involvement in Duchenne muscular dystrophy: an MR imaging and spectroscopy study. *Skeletal Radiol*. 2012;41(4):437–45.
10. Weber MA, Nagel AM, Wolf MB, et al. Permanent muscular sodium overload and persistent muscle edema in Duchenne muscular dystrophy: a possible contributor of progressive muscle degeneration. *J Neurol*. 2012;259(11):2385–92.
11. Lehmann-Horn F, Weber MA, Nagel AM, et al. Rationale for treating oedema in Duchenne muscular dystrophy with eplerenone. *Acta Myol*. 2012;31(1):31–9.
12. Karamitsos TD, Neubauer S. Cardiovascular magnetic resonance: a powerful diagnostic and prognostic tool in modern cardiology. *Prog Cardiovasc Dis*. 2011;54(3):179–80.
13. Finsterer J. Presence or absence of cardiac disease in Duchenne muscular dystrophy. *Cardiology*. 2012;121(3):184–5.
14. Spurney CF. Cardiomyopathy of Duchenne muscular dystrophy: current understanding and future directions. *Muscle Nerve*. 2011; 44(1):8–19.
15. •• Davidson ZE, Truby H. A review of nutrition in Duchenne muscular dystrophy. *J Hum Nutr Diet*. 2009; 22(5):383–93. *This study provides a broad, evidence based overview of multiple nutritional considerations in children with DMD. It can be utilized by the provider to create general nutritional management guidelines in their practice.*
16. Kley RA, Tarnopolsky MA, Vorgerd M. Creatine for treating muscle disorders. *Cochrane Database Syst Rev*. 2011;16(2): CD004760.
17. Mok E, Letellier G, Cuisset JM, et al. Lack of functional benefit with glutamine versus placebo in duchenne muscular dystrophy: a randomized crossover trial. *PLoS One*. 2009;4(5):e5448.
18. Mok E, Eleouet-Da Violante C, Daubrosse C, et al. Oral glutamine and amino acid supplementation inhibit whole body protein degradation in children with Duchenne muscular dystrophy. *Am J Clin Nutr*. 2006;83:823–8.
19. Hankard RG, Hammond D, Haymond MW. Oral glutamine slows down whole body protein breakdown in Duchenne muscular dystrophy. *Pediatr Res*. 1998;43:222–6.
20. Bertorini TE. *Neuromuscular disorders: treatment and management*. Philadelphia: Saunders Elsevier; 2011.
21. Martigne L, Seguy D, Pellegrini N, et al. Efficacy and tolerance of gastrostomy feeding in Duchenne muscular dystrophy. *Clin Nutr*. 2010;29:60–4.
22. Mizuno T, Komaki H, Sasaki M, et al. Efficacy and tolerance of gastrostomy feeding in Japanese muscular dystrophy patients. *Brain Dev*. 2012;34:756–62.
23. Diamanti A, Panetta F, Tentolini A. Efficacy and safety of gastrostomy feeding in Duchenne muscular dystrophy. *Clin Nutr*. 2011;30:263.
24. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15): 1218–26.
25. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. *Am J Respir Crit Care Med*. 2004;170:456–65.
26. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long term effect. *Am J Phys Med Rehabil*. 2005;84: 843–50.
27. Biggar WD, Gingras M, Fehlings DL, et al. Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr*. 2001;138:45–50.
28. Daftary AS, Crisanti M, Kalra M, et al. Effect of longterm steroids on cough efficiency and respiratory muscle strength in patients with Duchenne muscular dystrophy. *Pediatrics*. 2007;119:e320.
29. Buyse GM, Van der Mieren G, Erb M, et al. Long-term blinded placebo controlled study of SNT-MC17/idebenone in the dystrophin deficient mdx mouse: cardiac protection and improved exercise performance. *Eur Heart J*. 2009;30:116–24.
30. Buyse GM, Goemans N, van den Hauwe M, Meier T. Effects of glucocorticoids and idebenone on respiratory function in patients with Duchenne muscular dystrophy. *Pediatr Pulmonol*. 2012. doi: 10.1002/ppul.22688
31. Kwon SW, Kang S, Kim J, et al. Outcomes of cardiac involvement in patients with late-stage Duchenne muscular dystrophy under management in the pulmonary rehabilitation center of a tertiary referral hospital. *Cardiology*. 2012;121:186–93.
32. Markham LW, Kinnett K, Wong BL, et al. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2008;18:365–70.
33. Ogata H, Ishikawa Y, Minami R, et al. Beneficial effects of beta-blockers and angiotensin converting enzyme inhibitors in Duchenne muscular dystrophy. *J Cardiol*. 2009;53:72–8.
34. Kajimoto H, Ishigaki K, Okumura K. Beta blocker therapy for cardiac dysfunction in patients with muscular dystrophy. *Circ J*. 2006;70:991–4.
35. Viollet L, Thrush PT, Flanigan KM, et al. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the

- cardiomyopathy in Duchenne muscular dystrophy. *Am J Cardiol.* 2012;110:98–102.
36. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010;9:77–93.
  37. •• Merlini L, Gennari M, Malaspina E, Cecconi I, Armaroli A, et al. Early corticosteroid treatment in 4 Duchenne muscular dystrophy patients: 14-year follow-up. *Muscle Nerve* 2012; 45(6):796–802. *There has been significant discussion about the most appropriate timing for initiating the use of corticosteroid treatment, with current recommendations to discuss initiation when motor gains are often reaching a plateau between ages 4-6. In this study of boys with DMD, 4 of the 5 who began treatment with corticosteroids between 2-4 years of age were ambulatory at ages 17.0-18.5 years, which argues for the benefit of early initiation of corticosteroid treatment, and for the importance of long term studies to investigate the timing of initiation.*
  38. Kinali M, Arechavala-Gomez V, Feng L, Cirak S, Hunt D, Adkin C, et al. Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study. *Lancet Neurol.* 2012;8:918–28.
  39. Cirak S, Feng L, Anthony K, Arechavala-Gomez V, Torelli S, Sewry C, et al. Restoration of the dystrophin-associated glycoprotein complex after exon skipping therapy in Duchenne muscular dystrophy. *Mol Ther.* 2012;20:462–7.
  40. Percival JM, Whitehead NP, Adams ME, Adamo CM, Beavo JA, Froehner SC. Sildenafil reduces respiratory muscle weakness and fibrosis in the mdx mouse model of Duchenne muscular dystrophy. *J Pathol.* 2012;228:77–87.
  41. Gordon BS, Delgado Díaz DC, Kostek MC. Resveratrol decreases inflammation and increases utrophin gene expression in the mdx mouse model of duchenne muscular dystrophy. *Clin Nutr.* 2013;32(1):104–111. doi: [10.1016/j.clnu.2012.06.003](https://doi.org/10.1016/j.clnu.2012.06.003)
  42. Nabukera SK, Romitti PA, Campbell KA, Meaney FJ, Caspers KM, Mathews KD, Hockett Sherlock SM, Puzhankara S, Cunniff C, Druschel CM, Pandya S, Matthews DJ, Cifaloni E. Use of complementary and alternative medicine by males with Duchenne or Becker muscular dystrophy. *J Child Neurol.* 2012;27:734.