Duchenne Muscular Dystrophy: Canadian Paediatric Neuromuscular Physicians Survey

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ABSTRACT: *Background:* Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy in childhood. *Method:* To assess the current care of paediatric DMD patients in Canada, a questionnaire was mailed to 17 physicians who were members of the Canadian paediatric neuromuscular group. Areas of enquiry included; 1) multidisciplinary team composition; 2) means of DMD diagnosis; 3) corticosteroid use; surveillance and management for: 4) orthopaedic, 5) respiratory and 6) cardiac complications and 7) health maintenance (nutrition & immunizations). *Results:* Completed surveys were returned by 14/17 (82%) of physicians. Twelve respondents followed DMD patients. All centres had multidisciplinary teams, including respirology (11/12), child neurology or physiatry (11), physiotherapy (9), occupational therapy (9) and orthopaedic surgery (7). Deflazacort 0.9mg/kg/d was used at all centres, which was continued after loss of independent ambulation (11), along with routine calcium and vitamin D supplementation (10). Night splints were prescribed at all centres. Routine surveillance studies included pulmonary function testing (11), sleep studies (10), EKG/echocardiogram (10), bone density (DEXA) scans (10), spine radiography (9), and dietician referral (4). *Conclusion:* Paediatric DMD patients are receiving relatively consistent care in multidisciplinary clinics across Canada, in accordance with recommended guidelines for DMD.

RÉSUMÉ: Dystrophie musculaire de Duchenne : enquête auprès des pédiatres du Canadian Paediatric Neuromuscular Goup. *Contexte :* La dystrophie musculaire de Duchenne (DMD) est la forme la plus fréquente de dystrophie musculaire dans l'enfance. *Méthode :* Nous avons posté un questionnaire à 17 médecins membres du Canadian Paediatric Neuromuscular Group afin d'évaluer les soins actuels donnés aux patients d'âge pédiatrique atteints de DMD au Canada. L'enquête portait sur les aspects suivants : 1) la composition des équipes multidisciplinaires; 2) les moyens diagnostiques utilisés pour poser le diagnostic de DMD; 3) l'utilisation de corticostéroïdes; la surveillance et le traitement des complications 4) orthopédiques, 5) respiratoires et 6) cardiaques et 7) les soins de santé usuels (nutrition et immunisations). *Résultats :* Quatorze des 17 médecins (82%) ont retourné le questionnaire complété. Douze d'entre eux suivaient des patients atteints de DMD. Tous les centres avaient des équipes multidisciplinaires qui incluaient des pneumologues (11/12), des neurologues ou physiatres pédiatriques (11), des physiothérapeutes (9), des ergothérapeutes (9) et des orthopédistes (7). Tous les centres utilisaient le déflazacort à 0,9 mg/kg/j. Cette médication était maintenue après le passage au fauteuil roulant (11) ainsi que la prise de routine de calcium et de vitamine D (10). Des attelles nocturnes étaient prescrites dans tous les centres. La surveillance de routine comprenait des épreuves de fonction pulmonaire (11), des études du sommeil (10), un EKG/échocardiogramme (10), mesure de la densité osseuse (DEXA) (10), radiographie de la colonne vertébrale (9) et consultation en diététique (4). *Conclusion :* Les patients pédiatriques atteints de DMD reçoivent des soins relativement uniformes dans toutes les cliniques multidisciplinaires au Canada, conformément aux recommandations énoncées dans les lignes directrices sur la prise en charge de la DMD.

Duchenne muscular dystrophy (DMD) is caused by a mutation in the *DMD* gene, coding for dystrophin at Xp21. Inadequate or defective dystrophin protein causes increased muscle membrane fragility, resulting in proximal muscle weakness and marked elevation of serum creatine kinase (CK) levels. Boys with DMD typically present with gait abnormalities (toe-walking, frequent falls, delayed walking, exercise intolerance) between ages 3 - 5 years old, with progressive loss of independent ambulation occurring around 7 - 12 years-of-age. Most boys live until their late 20's, with death resulting from respiratory or cardiac complications. Corticosteroid therapy offers benefit to DMD boys by improving muscle strength and functional test scores[1-4], prolonging independent ambulation[5-9],

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improving pulmonary function tests[1,2], and delaying the onset of cardiomyopathy[10-12] and scoliosis[13,14].

Due to the progressive nature of DMD, affected individuals require regular monitoring and management of several areas: 1) muscle strength and function; 2) corticosteroid treatment and potential side-effects[1,15]; 3) orthopaedic issues such as soft-tissue contractures, fractures or scoliosis; 4) respiratory complications such as impaired secretion clearance or alveolar hypoventilation; 5) cardiomyopathy; 6) routine health maintenance and 7) social and emotional well being. Ideally patients with DMD should be followed in a comprehensive multidisciplinary neuromuscular clinic in order to minimize the need for patients and families to make multiple visits to various subspecialty clinics. Currently, no Canadian guidelines exist for the care or surveillance of DMD patients. As a result, Canadian clinicians must turn to several other sources for recommendations including: American Academy of Neurology and Child Neurology Society (practice parameter for corticosteroid use in DMD patients)[16]; American Thoracic Society (DMD respiratory care recommendations)[17], American Academy of Pediatrics (DMD cardiac surveillance recommendations)[18] and the European TREAT-NMD (DMD comprehensive care pathway)[19].

This study was part of a collaborative effort to understand, and ultimately improve, the standard of care for Canadian DMD patients. It was aimed at determining the current clinical management of DMD in paediatric neuromuscular centres across the country in the context of the existing practice guidelines.

METHODS

A five-page questionnaire was developed by the authors for the purpose of surveying members of the Canadian paediatric neuromuscular group (CPNG) to determine the current standard of care for DMD in Canada. The CPNG is a group of Canadian clinicians (comprised of child neurologists, physiatrists, developmental paediatricians and consultant paediatricians) who have an interest and expertise in caring for children with neuromuscular disorders. All CPNG physicians have a professional affiliation with a tertiary care paediatric hospital or rehabilitation centre. The CPNG first met in 2005, and currently meets twice each year to discuss issues pertaining to patient advocacy and education, current clinical trials, and future research opportunities.

Ethics approval was obtained by the University of Calgary, Conjoint Health Research and Ethics Board (institution of JKM, senior author). The questionnaire contained items summarized into seven main categories pertaining to the care of DMD patients. The 17 CPNG members were mailed a copy of the questionnaire. Members who did not return the questionnaire after two months were contacted twice as a reminder.

RESULTS

Respondents

Completed questionnaires were returned by 14/17 (82%) of physicians. Twelve respondents indicated that they followed DMD patients. These respondents completed all portions of the questionnaire. All regions of Canada were represented among respondents, including western Canada (5), Ontario (7), Québec (1) and eastern Canada (1). Physicians following DMD patients

described their scope of practice as child neurology (8/12), physical medicine and rehabilitation (3/12) or developmental paediatrics (1/12). The mean length of time in practice was 17.8 yrs (range: 4 - 41 yrs).

1. Multidisciplinary teams

All respondents (12/12) followed DMD patients in a multidisciplinary care setting. Multidisciplinary teams were comprised of: respirology (11/12), neurology or physiatry (11/12), social work (10/12), clinic nurse (9/12), occupational therapy (9/12), physiotherapy (9/12), orthopaedic surgery (7/12), cardiology (4/12), general paediatrics (4/12) and/or dietician (3/12). Five respondents followed only paediatric DMD patients (<18yrs old) while seven followed both paediatric and adult DMD patients.

2. DMD diagnosis

Genetic testing for dystrophin gene deletions or duplications is the initial diagnostic test ordered at all centres for males presenting with suspected DMD. Centres indicated that they may order 1) multiplex polymerase chain reaction with florescent in-situ hybridization probes, or 2) multiple ligation-dependent probe amplification. Complete DMD gene sequencing is used at some centres if initial genetic testing is negative.

Muscle biopsy is performed at 11/12 centres when genetic testing fails to detect a dystrophin gene mutation in a clinically symptomatic male. Genetic counselling was routinely offered at all centres with the aim of: 1) identifying asymptomatic female carriers to facilitate cardiac surveillance, and 2) providing counselling regarding recurrence risk for immediate and extended family members.

3. Corticosteroids

Deflazacort (0.9mg/kg/d) was used at all centres. Two respondents indicated that they occasionally used prednisone (0.75mg/kg/d) for treatment of some patients. Respondents indicated some variability with regard to the start of corticosteroid therapy. Most centres used patient's age as a criteria for initiating treatment, around three to five years (3/12) or six to eight years (4/12) of age. No centre routinely started corticosteroid therapy after eight-years-old. One centre initiated treatment at the time of DMD diagnosis. Others (3/12) used qualitative functional assessment (i.e. "increased gait difficulties and falling") as a means for treatment initiation. One respondent indicated that treatment was initiated after "discussion with caregiver" at any of the age intervals listed above. Corticosteroid therapy was continued indefinitely by most clinicians (11/12), even after patients became unable to ambulate independently.

Calcium and vitamin D supplementation were routinely recommended at most centres (10/12) when DMD patients started corticosteroid therapy. The dose of recommended calcium supplementation varied from 600-1200 mg/day and vitamin D 200-1000 IU/day. One respondent recommended oral creatine and salbutamol routinely. Whey protein supplements were recommended at another centre.

Routine bone densitometry (DEXA scan; dual energy X-ray absorptiometry) was offered at 10/12 centres. These centres obtained baseline DEXA scans prior to starting corticosteroid

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therapy with surveillance scans completed at 6-24 month intervals. One centre indicated that inadequate resources precluded their ability to obtain bone densitometry. If bone demineralization was identified, 6/12 respondents indicated they would consult endocrinology for possible bisphosphonate therapy (alendronate, pamidronate or zoledronate). Several clinicians (3/12) indicated they would manage bisphosphonate administration independently.

4. Orthopaedics

Respondents indicated that orthopaedic surgery was part of over half (7/12) of all multidisciplinary teams. Teams without orthopaedics had either physiatry (3/12), combined physical and occupational therapy (1/12) or physiotherapy alone (1/12) to monitor and treat soft-tissue contractures, assess mobilization and monitor for scoliosis. Overall, allied health members were well represented on most multidisciplinary teams with physiotherapy (9/12) and occupational therapy (9/12) being the most common.

Night splints were routinely offered at all centres (12/12). Splints use was started between ages three to ten years for managing fixed plantar flexion contractures from tight Achilles tendons. Most centres (9/12) offered routine, surveillance radiographs for scoliosis. The onset of surveillance at each centre was not specified.

5. Respiratory

Respirology was the most consistent member of the multidisciplinary team (11/12), reflecting the importance of the respiratory system in this progressive muscle disease. The one team lacking respirology indicated that they independently monitored pulmonary function tests (PFT) and referred to respirology when PFT abnormalities were detected.

Routine, anticipatory PFT was offered at 11/12 centres starting between ages 6-11 years-old, and followed at 6-12 month intervals. One centre began PFT testing when DMD patients became symptomatic for respiratory difficulties. Sleep evaluation studies were routinely performed at 10/12 centres. Four respondents indicated that they used age-criteria with the time of the first study varying from 7 years old to 12-16 years-old. Four respondents offered sleep studies when varying degree of PFT abnormalities were detected (i.e. Forced vital capacity (FVC) <80% predicted value or FVC <1L). Two centres indicate that they offer routine sleep study evaluations when patients present with symptoms of nocturnal hypoventilation (i.e. day-time somnolence, morning headaches and fatigue). Two centres did not offer routine sleep study evaluations. Breath stacking and cough-assist techniques (manual or mechanical) were offered at 9/12 centres.

6. Cardiac

Respondents indicated that cardiology was not typically a member of multidisciplinary teams. Teams lacking cardiology (8/12) indicated that cardiology referrals were initiated at the time of initial diagnosis (6/8), when surveillance testing indicated electrocardiogram (EKG) or echocardiogram abnormalities (1/8) or when the child reached ten-years-old (late-ambulation stage) (1/8).

Electrocardiogram and echocardiograms were most often ordered and followed directly by cardiologists (10/12) whether or not they were part of the DMD multidisciplinary team. Studies were completed at one to two years intervals. Holter monitoring was not part of surveillance studies at any centre and was requested only if there was a clinical history of symptomatic cardiac arrhythmias.

7. Health Maintenance

Pneumococcal and influenza vaccinations were routinely recommended by 11/12 respondents. Varicella vaccination was also commonly recommended (10/12). Registered dieticians were routinely involved in patient care at 4/12 centres.

This questionnaire did not ask CPNG members about the timing or details surrounding the discussion of end-of-life issues with DMD patients and families (i.e. long-term mechanical ventilation via tracheostomy versus palliation). All respondents indicated that palliative care was not a routine part of the multidisciplinary clinic team.

DISCUSSION

As evident from the survey responses, children with DMD appeared to be receiving relatively consistent care across Canada. Based upon the results of the questionnaire, the following discussion will focus on the clinical practise in Canada within the context of existing evidence and/or guidelines.

1. Multidisciplinary teams

Multidisciplinary teams provide patients with the benefit of receiving multiple sub-specialist opinions at one clinic visit. This has the effect of 'stream-lining' and optimizing patient care. Respondents have indicated that multidisciplinary clinics are commonplace at all Canadian paediatric tertiary care centres.

2. Duchenne muscular dystrophy diagnosis

Duchenne muscular dystrophy males may possess a dystrophin gene with; 1) large deletion (65% cases); 2) duplication (5-10% cases) or; 3) point mutations (25-30% cases)[20]. Large deletions are readily detectable (98% cases) by polymerase chain reaction with subsequent florescent in situ hybridization, especially at one of two regions or "hot-spots" (i.e. exons 2-20 and 44-53) where deletions are more likely to occur. Large deletions at other locations, duplications and point mutations will not be detected by this method, and require either multiplex ligation-dependent probe amplification, muscle biopsy or dystrophin gene sequencing for confirmation of diagnosis. Emerging DMD treatments are becoming increasingly tailored to genotype-specific patients (i.e. PTC124 for premature stop codon suppression, or exon skipping using antisense oligonucleotides) and treatment efficacy may hinge upon the type of mutation[21]. Obtaining complete *DMD* gene sequencing remains a time-consuming process, requiring government pre-approval for out-of-province testing in all provinces except Ontario. Fortunately, the results of this survey indicate that Canadian clinicians are pursuing this important step when *DMD* gene deletions/duplications cannot be identified.

3) Corticosteroids

Prednisone and deflazacort are both accepted therapies offered to boys with DMD[16]. Deflazacort, a synthetic derivative of prednisolone, is not approved by Health Canada for use in DMD patients; however, it can be obtained in this country through a government Special Access Program. In the United States, deflazacort lacks Food and Drug Administration (FDA) approval and must be obtained from out-of-country suppliers.

Eight published randomized controlled trials (Table 1) have demonstrated corticosteroids to improve DMD patient muscle strength and timed function tests. This includes seven randomized trials of prednisone (or prednisolone) versus placebo[1-3,22-25] and 1 deflazacort versus placebo trial[9].

Several prednisone doses (0.3mg/kg; 0.75mg/kg; 1.5mg/kg) and schedules (daily, alternate days; 10 days/month) have been studied. Daily prednisone 0.75mg/kg/day is currently accepted as the optimal dose, providing the best balance of therapeutic benefit relative to the potential for steroid-related side-effects[16]. Daily deflazacort at 0.9mg/kg/day is an accepted alternative to prednisone[16,19], and may offer a more favourable side-effect profile[4,5,15]. There have been two randomized studies directly comparing deflazacort to prednisone (0.75mg/kg)[15,26,27], but the reporting of these trials does not allow conclusive determination of either drugs superiority in DMD.

Mendell et al (1989)[1] provided the first, large, randomized control of daily prednisone (0.75mg/kg and 1.5mg/kg) versus placebo. Both high and low prednisone doses were associated with an improvement of timed functional testing, as early as one month after treatment onset. At six months (end-point of study), both prednisone groups showed similar benefit to muscle strength, function and PFT versus placebo. The higher prednisone dose (1.5mg/kg) did not confer additional functional benefit, but instead was associated with a higher incidence of side effects such as cushingnoid features, hirsutism, and weight gain. Fenichel et al (1991)[3] followed these same DMD patients for an additional six months to assess the effect of alternate-day prednisone dosing. The former-placebo group was given prednisone (2.5mg/kg) every other day, while the former-daily prednisone groups (0.75mg/kg and 1.5mg/kg) were changed to alternate-day prednisone (1.25mg/kg and 2.5mg/kg). Each group demonstrated deterioration of muscle strength with alternate-day treatment at six months.

Griggs et al (1991)[2] provided a randomized controlled trial comparing two lower doses of daily prednisone (0.75mg/kg and 0.3mg/kg) versus placebo. Again, both prednisone doses was associated with improved muscle strength, function and PFT, as early as ten days after treatment initiation. However, by three months individuals receiving prednisone 0.75mg/kg were significantly stronger than the 0.3mg/kg group. This study was influential at establishing prednisone 0.75mg/kg as the recommended treatment dose for DMD patients in the United States[16]; however it is noteworthy that the 0.75mg/kg dose was associated with a higher incidence of side-effects.

Four additional randomized, placebo-controlled studies have demonstrated a clear therapeutic benefit to prednisone: Beenakker et al (2005)[25] studied prednisone 0.75mg/kg for first ten days per month; Backman et al (1995)[23] used daily prednisolone 0.35mg/kg; Rahman et al[24] studied daily prednisolone 0.75mg/kg; and Griggs et al (1993)[22] used daily

prednisone 0.3mg/kg & 0.75mg/kg. All studies demonstrated improvement in muscle strength and timed functional test in the steroid group relative to placebo. Griggs' study was the longest in duration; it showed that the initial benefit seen with daily prednisone therapy persisted at 18 months, and the addition of azathioprine to some patients during the last 12 months of treatment did not confer any additional benefits[22].

Deflazacort has been the subject of two controlled trials comparing to placebo. The first non-randomized trial[4] compared daily deflazacort (1mg/kg) to placebo for nine months. Deflazacort-treated patients were stronger by three months, with improvement in their timed Gower's manoeuvre evident by six months, and the differences increased by nine months. Side effects of deflazacort included behaviour changes, increased appetite, cushingnoid appearance and hirsutism. Excessive weight gain (i.e. >20% of baseline) was less pronounced with daily deflazacort (7%) relative to studies with daily prednisone, but this data has yet to be confirmed by a large direct comparison trial[16]. The second randomized trial[9] provided a longer-term (24 month) evaluation of alternate day deflazacort (2mg/kg) versus placebo. This group confirmed superior muscle strength and functional testing in the deflazacort group (within six months) which was sustained at 24 months. In this study, deflazacort-treated patients had an average weight gain of only 11.4% compared to 7.5% for the placebo group.

Only two small trials have directly compared daily deflazacort (0.9mg/kg) with daily prednisone (0.75mg/kg)[15,26,27]. Bonifati et al[15] reported no statistical difference in the efficacy of the two drugs after 12 months treatment, and a trend in less weight gain was seen with deflazacort (9% compared to 21.3% increase with prednisone)[15]. The second trial was never published beyond interim results[26,27]. Clearly there is a need for a large, multi-centre trial directly comparing the therapeutic benefit and side-effect profile of deflazacort and prednisone. Until then, systematic reviews[28], meta-analysis[29] and medical societies[16] have recommended either daily prednisone (0.75mg/kg) or deflazacort (0.9mg/kg) for maintaining muscle strength and function for individuals with DMD.

Corticosteroids: Benefits beyond strength

There is mounting evidence that the benefit of corticosteroids extends beyond skeletal muscle. Prednisone and deflazacort have been shown to improve pulmonary function tests[1,2,13]; delay the onset and/or decrease the incidence of cardiomyopathy[10-12]; and scoliosis[13,14]. Biggar and his colleagues provided evidence from both prospective[13] and retrospective studies[5,10], including one of the best longitudinal prospective data on a cohort of DMD boys. Fifty-four individuals received either daily deflazacort 0.9mg/kg (30 patients) or no treatment (24 patients), and were followed for a mean of 7.2yrs (treatment group) and 7.4yrs (control group). The results showed that deflazacort-treated DMD boys had a striking improvement in muscle strength, pulmonary function as well as a marked reduction in the incidence of scoliosis. The mean age that deflazacort-treated patients stopped walking was 12.3yrs (versus 9.8 yrs in controls). The deflazacort group had a mean FVC of 72% predicted (range 50-88%) versus 35% predicted (range: 20-48%) for controls. Scoliosis (curve >20º) was much less common in deflazacort-treated boys (5/30, 17%) compared to controls (16/24, 67%)[13]. Deflazacort-related side-

effects in the treatment group included weight gain (mean of 3.7 kg more than control group), osteopenia and symptomatic stress fractures (10%), and asymptomatic cataracts (33%)[13].

Corticosteroids: When to initiate therapy

There are no randomized controlled trials on the optimal age for initiating corticosteroid therapy in DMD. This lack of information may explain the variability seen among our survey respondents as to when steroid therapy is initiated. Most studies have included corticosteroid use for DMD boys between 5-15 years old[1-3]. One small, open-label, prospective cohort study examined younger (2-4 yrs old) DMD boys treated with prednisone (initially 0.75mg/kg daily; x 2 weeks; then 1.25 mg/kg on alternate days). After 55 months treatment, all patients in the prednisone group were still able to rise from the floor, whereas 2/3 of the control patients had lost that ability[30]. Another prospective uncontrolled study of six boys under five years of age treated with intermittent prednisone (ten days per month) reported an improvement of muscle strength and functional testing, compared to the natural history of untreated young DMD boys[31]. The sample size for these two studies was extremely small (five to six patients each). This finding points to the need for future studies to better delineate the optimal age for initiating corticosteroid treatment.

Corticosteroids: When to discontinue therapy

The issue of when to discontinue corticosteroid therapy is also controversial. Our survey found that almost all responding Canadian neuromuscular specialists continued deflazacort indefinitely for DMD individuals even after losing independent ambulation. This practice may be due to the results of several retrospective, open-labelled cohort studies indicating deflazacort treatment to be associated with delayed onset of late complications (listed above). Continuing corticosteroid therapy for the potential benefit of delaying cardiomyopathy and respiratory failure must be balanced with ongoing bone demineralization, a serious concern for the non-ambulatory, non-weight bearing patient. The potential for substantial weight gain and its accompanying morbidity (i.e. increased incidence of obstructive sleep apnea, worsening hypoventilation, increased challenge for caregivers surrounding patient transfers) are other reasons for caution. Further prospective studies are needed to evaluate the risk-benefit ratio of corticosteroid use in non-ambulatory DMD males.

Corticosteroids & monitoring bone health

Ensuring optimal bone health with adequate calcium and vitamin D intake is an important consideration, since corticosteroid therapy appears to increase the risk of vertebral fracture in DMD patients, which may occur following minor or no identifiable trauma[32]. A recent DMD workshop (Cincinnati, USA)[33] acknowledged that while vitamin D and calcium contribute to bone health, supplementation has not been proven to reduce the risk of low-impact fractures among DMD boys. Experts recommended that clinicians check serum 25-hydroxyvitamin D levels annually and offer supplementation for levels <20ng/mL[33]. In contrast, current European guidelines recommend routine supplementation with calcium (4-8 yrs old:

800mg/d; 9-18 yrs old: 1300mg/d) and vitamin D (400 IU/d) if dietary intake is inadequate[19]. Our survey demonstrates that most Canadian DMD centres follow the European guidelines by recommending vitamin D and calcium supplementation at the initiation of steroid therapy.

Expert recommendations from another DMD workshop (Birmingham, UK)[32] recommended bone densitometry or DEXA scan (dual energy X-ray absorptiometry) in all DMD patients at one to two year intervals[32]. However, there is no consensus as to what skeletal sites should be studied (i.e. hip, femur, lumbar vertebrae, total body) or what Z-score threshold might trigger the initiation of bisphosphate therapy[33]. Duchenne muscular dystrophy boys have delayed growth and puberty as well as diminished muscle mass, all of which may contribute to potentially lower age-matched bone-density scores[33]. Although most Canadian DMD centres obtain routine bone density studies (every 6-24 months), further studies are needed to identify reliable predictors for non-traumatic fractures in DMD patients[33].

Other therapies

Limited benefits for DMD patients has been demonstrated with several other drugs such as creatinine monohydrate[34], salbuterol[35,36] and cyclosporine[37]. No therapeutic benefit has been found with use of: anabolic steroids (oxandrolone)[38], allopurinol[39], glutamine[40], selenium or vitamin E[41]. A clinical trial of PTC124 a nonsense mutation read-through agent (Ataluren™, PTC Therapeutics Inc., Cambridge, MA) is currently underway for DMD and Becker Muscular Dystrophy (BMD) boys known to have a nonsense mutation (premature stop codon). If effective, this drug would offer benefit to only a subgroup of DMD patients. In our study only one respondent routinely uses creatine monohydrate and salbuterol, reflecting the need for more studies to determine their clinical relevance.

4. Orthopaedics

Scoliosis is a common complication of DMD[20,42]. Most individuals with DMD develop scoliosis with loss of independent ambulation[14]. An early, natural history study of 33 DMD boys who did not receive spinal fusion, revealed their scoliosis to progress to a mean curvature of 89.6 + 33.7° at the time of death[42]. Some experts have recommended surveillance spine radiography be conducted every six months during adolescence[43], however, no consensus guidelines exist. Scoliosis contributes to the deterioration of respiratory function in DMD patients, with an estimated 4% loss of forced vital capacity for every 10° progression of the Cobb angle[44]. Scoliosis surgery delays further deterioration of pulmonary function and may improve long-term survival[45]. It also improves patient comfort and facilitates sitting, transfer, and personal care. However, scoliosis surgery may not reverse the loss of vital capacity[46].

Due to progressive weakness, DMD patients do not benefit from non-surgical interventions such as bracing for scoliosis[47]. Instead, spinal fusion is often performed at early stages (with radiographic deformity as slight as 10-20°)[48]. The rate of all operative and post-operative complications (i.e. skin infection or pneumonia, pleural effusion, cardiac arrest, need for long-term

ventilation and tracheostomy, hardware malfunction) in DMD boys undergoing scoliosis surgery is approximately 10-30%[48,49].

A FVC of 30-40% was once referred to as a "cut-off" for DMD scoliosis surgery, due to increased cardiorespiratory morbidity associated with further respiratory weakness however, a recent retrospective study led to a revision of this thinking[49]. Marsh et al[49] reviewed the complications of scoliosis surgery among 30 DMD patients with a range of FVC (18-60%). Patients were grouped according to their pulmonary function: 17 patients had FVC >30%; 13 patients were <30%. The two groups demonstrated no difference in complication rate, time in the operating suite, duration of post-operative ventilator support or duration of inpatient stay. Other studies have demonstrated clinical benefit for scoliosis surgery in DMD patients with severe respiratory muscle weakness, including those with FVC <30% predicted[49], although the best prognosis occurs for patients with FVC > 40%[42].

The American Thoracic Society (ATS) has stated that FVC values alone should not represent an absolute contraindication to scoliosis surgery[17]. Prior to surgery, all DMD patients should be evaluated by a respirologist[17], receive a complete cardiac evaluation including echocardiogram even if no symptoms of cardiac failure are clinically evident[16], and have pre-operative consultation from anaesthesiology.

5. Respiratory

Duchenne muscular dystrophy patients experience a gradual loss of respiratory muscle strength over time. The onset of hypoventilation and subsequent need for ventilation is associated with loss of independent ambulation[50]. Patients first develop ineffective and weak cough followed by increasing alveolar hypoventilation and eventually respiratory failure, which is the cause of death for roughly 90% of DMD patients[20].

The ATS recommends that DMD patients should be seen by a respirologist for anticipatory medical guidance and baseline pulmonary function testing early in the course of their disease (i.e. age 4-6 yrs)[17]. Follow-up frequency should be increased to six monthly intervals, either: 1) beginning at 12 years-of-age, 2) after loss of independent ambulation, or 3) after decline in FVC<80% predicted[17]. Patients requiring use of mechanically assisted airway clearance therapy or mechanically assisted ventilation should also be seen by respirology every three to six months.

Our survey indicated that sleep studies are not widely performed across Canadian centres, in part related to inadequate resources. The ATS recommends annual evaluation for sleep-disordered breathing for all DMD patients starting from the time that they are wheelchair-bound and/or when clinically indicated. This should include annual polysomnography or overnight pulse oximetry with continuous CO_2 monitoring[17]. Early detection and treatment of nocturnal hypoventilation and CO_2 retention may improve daytime quality of life and delay the onset of pulmonary hypertension. Nocturnal non-invasive ventilation using bi-level positive airway pressure (BiPAP) is typically the first step in providing respiratory support for DMD patients with deteriorating respiratory function. The advent of non-invasive ventilation in the 1990's has significantly increased the life expectancy of DMD males, with the mean life expectancy now at 25.3 years[51].

Individuals with DMD are at increased risk of atelectasis and subsequent pneumonia when they are no longer able to generate a sufficient cough to clear their airways. As DMD patients are typically unaware of this issue, cough effectiveness should be assessed regularly by measuring maximal inspiratory and expiratory pressures, peak cough expiratory flow, and forced vital capacity[17]. Almost all Canadian centres follow pulmonary functions routinely, with most offering cough assist and breath-stacking support. Current recommendations suggest that cough assist devices be employed for all DMD patients with peak cough flow <270 L/min and/or maximal expiratory pressure less than 60cm H_2O[17].

6. Cardiac

Nigro et al (1990)[52] has provided one of the best studies documenting the natural history of cardiac disease among DMD patients. A group of 328 DMD patients were followed between 3-11 years. Pre-clinical cardiac involvement was reported in 25% of patients under six-years-old, increasing to 59% between six to ten-years-old. Clinically apparent cardiomyopathy was first noted after age ten years, and was present in all DMD patients over 18-years-old. Cardiac failure is the cause of death in 10-20% of DMD males[50]. Right ventricular failure may also develop from respiratory failure and pulmonary hypertension.

The onset of dilated cardiomyopathy may precede clinical signs of heart failure (i.e. chest pain, palpitations or dyspnea) by several years. Symptoms of early cardiac failure may be more difficult to recognize in DMD patients due to skeletal muscle weakness and overall physical inactivity. One retrospective study suggests that early corticosteroid therapy may have the added benefit of delaying the onset of left ventricular (LV) dysfunction[12]. Another randomized controlled trial demonstrated a beneficial effect associated with the early, prophylactic use of the angiotensin converting enzyme inhibitor (ACE-I) perindopril[53]. The onset and subsequent progression of left ventricle dysfunction was less in DMD boys treated with prophylactic perindopril compared to placebo-controls[53].

After echocardiogram evidence of cardiomyopathy becomes apparent, sustained improvement in LV dysfunction has been reported in several retrospective studies with the use of another ACE-I (enalapril)[54] or combination of an ACE-I (enalapril or lisinopril) and a β-blocker (metoprolol or bisoprolol)[55,56]. The results from these studies, however promising, must be interpreted with caution. Data was collected retrospectively and did not compare treatment groups to a no-treatment control or natural history population. Furthermore, the studies did not specify if DMD patients were previously or currently treated with corticosteroids. Importantly, randomized, placebo-controlled trials may never be done in this area. Since ACE-I have been demonstrated to be beneficial for the treatment of adult non-DMD cardiomyopathy[57], the withholding of these potentially beneficial medications for a control group of DMD boys with cardiomyopathy would be difficult to justify on moral grounds.

Currently, the American Academy of Pediatrics (AAP)[18] recommends that ACE-I, β-blocker or diuretics should be considered when signs or symptoms of cardiac dysfunction are identified[18]. Additional data will be required before routine, early, or prophylactic ACE-I therapy be recommended. Expert

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Table 1: Published data on DMD patient care: levels of evidence (American Academy of Neurology Criteria)[58]

	Studies	Evidence level
Corticosteroid use (DMD boys; age 5-15 yrs old):		
Prednisone beneficial to muscle strength, motor function tests	7 Class I [1-3,22-25]	A
Deflazacort beneficial to muscle strength, motor function tests	1 Class I [9]	A
	1 Class II [4]	
Prednisone (0.75mg/kg/d) & deflazacort (0.9mg/kg/d) equally effective	2 Class I [15, 59]	A
Deflazacort has less weight gain (versus prednisone)	1 Class I [15]	A
Corticosteroids prolongs time of independent ambulation	1 Class I [13]	A
	1 Class II [8]; 3 Class III [5,6,10]	
Corticosteroids improve pulmonary function tests relative to placebo	2 Class I [1,2]	A
	1 Class II [13]	
Corticosteroids delay onset of cardiomyopathy	3 Class III [10-12]	B
Corticosteroids delay onset of scoliosis	1 Class II [13]	B
	1 Class IV [14]	
Calcium and vitamin D supplementation reduces bone demineralization	Expert opinion [19]	U
Bone densitometry (DEXA scan) every 1-2 yrs	Expert opinion [32]	U
Corticosteroid use (DMD boys; age <5 yrs):		
Prednisone prolongs proximal strength (ability to get up from floor)	1 Class II [30]	U
Prednisone (intermittent) improves motor function testing	1 Class III [31]	U
Scoliosis:		
Scoliosis surgery (Cobb angle >20°) improves FVC and peak expiratory flow	1 Class II [45]	B
Respiratory:		
Respirology evaluation (inc. exam, pulmonary function test) at 4-6 yr old	Expert opinion [17,18]	U
Respiratory evaluation q6mos at 12yr old, when not walking, or FVC <80%	Expert opinion [17]	U
Annual polysomnography with continuous CO_2 monitor or overnight oximetry	Expert opinion [17]	U
Cough-assist device should be considered if impaired airway clearance, peak cough flow <270 L/min or max expiratory pressure <60 cm H_2O	Expert opinion [17]	U
Cardiac:		
Annual cardiac evaluation (exam, EKG, echo) beginning at school-age	Expert opinion [17]	U
Bi-annual cardiac evaluation until 10yrs old, annual after 10yrs old	Expert opinion [18,19,50]	U
Enalapril therapy of DMD cardiomyopathy results in sustained left ventricle function	1 Class IV [54]	U
Combined ACE-I + β-blocker therapy results in sustained left ventricle function	1 Class III [55]	U
	1 Class IV [56]	
Early, prophylactic perindopril may delay onset & progression of Left ventricle dysfunction	1 Class I [53]	A
Routine holter monitoring only if cardiac dysfunction detected	Expert opinion [18]	U
Health maintenance:		
Routine nutrition monitoring and /or deflazacort use may reduce weight-gain	1 Class II [4]	C
Routine pneumococcal, varicella, influenza vaccines (prior to steroids)	Expert opinion [17]	U

Classification of studies:
Class I: Evidence provided by prospective, randomized control trial with marked outcome assessment and all of:
  i) primary outcome clearly defined;
  ii) exclusion/inclusion criteria clearly defined;
  iii) adequate account of drop-outs / crossover patients that are sufficiently low to not bias results;
  iv) relevant baseline characteristics between treatment and placebo groups.

Class II: Evidence provided by prospective matched group cohort study in representative population with marked outcome
  assessment that meets (i - iv, above) OR randomized control trial in representative population lacking 1 criteria (i - iv)
Class III: Evidence for all other control trials, including well-defined natural history control or patients serving as own
  controls in a representative population where outcome assessment is independent of patient treatment.
Class IV: Evidence for uncontrolled studies, case series, case reports or expert opinions.

Translation of evidence to recommendations:
Level A: Establishes treatment as **effective/ineffective/harmful** for specified population
  Requires at least 1 convincing Class I study or at least 2 Class II studies
Level B: Establishes treatment as **probably** effective/ineffective/harmful for specified population
  Requires at least one convincing Class II study or at least 3 consistent Class III studies
Level C: Establishes treatment as **possibly** effective/ineffective/harmful for specified population
  Requires at least 2 convincing & consistent Class III studies
Level U: Data is **inadequate or conflicting** given current knowledge

opinion from American and European groups recommend that all DMD patients receive a complete cardiac assessment at diagnosis, every two years until age ten years old, and annually thereafter[18,50]. Although paediatric cardiologists are frequently not members of Canadian DMD multidisciplinary teams, almost all centres refer patients to cardiology at the time of initial diagnosis. Cardiac follow-up becomes more frequent with advancing age, when the risk of underlying cardiomyopathy increases. Cardiology consultation may operate outside of the team due to the need for concomitant, EKG and echocardiogram testing that may not be easily integrated into the team visit. Given the need for these important surveillance studies, many Canadian centres opt to schedule cardiology visits at separate times.

Holter monitoring is not a routine part of cardiac surveillance; however, the AAP recommends periodic Holter monitoring for: 1) DMD patient with symptoms of possible cardiac arrhythmia (e.g. palpitations, chest pain), or 2) DMD patients with

Table 2: Summary of suggested DMD patient management: clinical practice guidelines[16-19,50]

Key Stages & Intervention	At diagnosis or early stage (2 to 7 years old)	Loss of ambulation / adolescence (8 to 16 years old)	Later stages (>16 years old)
Patient / family knowledge:	**Discuss:** DMD natural history, genetics / Role of corticosteroids / Research studies / Genetic counselling referral (Carrier testing if indicated) / Provide written material, websites and peer support information / Muscular Dystrophy Canada (MDC) contact information	**Discuss:** Nutrition / Complications of DMD (scoliosis, cardiac, and respiratory) / Complications of corticosteroids / Symptoms of nocturnal hypoventilation / Options for long-term ventilation assistance (i.e. BiPAP, CPAP) / Medical management of cardiomyopathy (if present) / School / social supports / Respite / financial issues / Adolescent needs, quality of life issues / Review previous topics	**Discuss:** Transition to adult care / Options for long-term ventilation support / Nutritional support (G-tube) / End-of-life counseling and advance medical directive / Review previous topics
Professional support	**Medical consultations:** Genetics / Respirology / Orthopedics (night splints, scoliosis) / Cardiology / Neurology / Physiatry / Ophthalmology (cataracts) / **Allied health support:** Clinic Nurse — Dietician / Physiotherapist — Psychologist / Occupational therapy / Social worker / MDC community liaison	**Medical consultations (as before, plus)** Endocrinology (osteoporosis, bisphosphonate therapy) / **Teach:** Chest physiotherapy to family / Breath stacking, cough assist / Seating for wheelchair / Passive & active exercises	**Medical consultations (as before)**
Medical therapy:	**Immunizations:** Varicella vaccine / Pneumococcal vaccine / Influenza vaccine / **Corticosteroids** Deflazacort (0.9mg/kg/d) or Prednisone (0.75mg/kg/d) / **Physiotherapy:** Passive stretching, night splints / **Bone health:** Calcium supplementation / Vitamin D supplementation / **Other:** Behavioral intervention / Weight management	**Review previous topics** **Interventions** (as required): Angiotensin converting enzyme inhibitor and/or beta-blocker (cardiomyopathy) / Diuretics (congestive heart failure) / Antibiotics (respiratory tract infections) / Sitting ankle-foot orthosis / Scoliosis surgery (pre-op Cardiology, Respirology & Anesthesiology consults)	**Review previous topics**
Monitoring: **Clinical:**	Weight and height, BP monitoring / Formal muscle function, strength tests / ECG, electrocardiogram (q 2 yrs) / Pulmonary function testing / Wrist x-ray for bone age / Bone densitometry study	**Same as before, except:** ECG, echocardiogram (q 1 yr) >10 yr old	**Same as before**
Laboratory:	Urine glucose / 25-hydroxyvitamin D level	**Same as before, plus:** PCO_2 measurement as needed	**Same as before**
Clinical review:	**6-12 months**	**3-6 months**	**1-3 months**

significant cardiomyopathy[18]. A prospective, cohort study revealed that frequent ventricular premature complexes (>6 / hour) and/or left ventricular dysfunction were associated with an increased risk of sudden death[60]. The fibrous replacement and/or dilatation of myocardial muscle fibres have been postulated to be the cause of ventricular tachyarrhythmia in such patients[60]. Early detection and institution of medical therapy (anti-arrhythmics or ACE-I) may be of potential therapeutic benefit.

Cardiac complications among female carriers

Female DMD carriers may present with muscle weakness and/or cardiomyopathy. Dilated cardiomyopathy may be the first and only manifestation of a *DMD* gene mutation in some female carriers, as marked cardiac involvement may occur in the absence of skeletal muscle weakness[61]. Serum CK is not a reliable means of screening for potential female carriers of mutated *DMD* genes, since elevated CK (2-10x normal) was only seen in 53% females with DMD-relatives and 30% females with BMD-relatives[62].

Hoogerwaard et al (1999) also provided one of the best prospective cohort studies of female DMD carriers; obligate female carriers (ages 18-58 yrs old) who had male relatives affected by either DMD (84) or BMD (43). At the time of evaluation, most carrier females (76%) were asymptomatic, while others reported myalgias or cramps (5%) or mild-to-moderate (9.5%) weakness on strength testing. Complete cardiac evaluation of these women with male DMD relatives found that 8% (7/84) had echocardiogram evidence for dilated cardio-myopathy and 19% (16/84) had left ventricle dilatation. Results for female carriers with male BMD relatives were similar, except that echocardiogram evaluation demonstrated that none had dilated cardiomyopathy, and 16% (7/35) had left ventricular dilation[62].

In light of female carriers having increased risk for skeletal and cardiac muscle involvement, the AAP recommends all female carriers to receive an initial cardiology assessment by late-adolescence, with repeat cardiac evaluation subsequently every five years, beginning at 25-30 years old[18].

7. Health Maintenance

The ATS recommends that all DMD patients receive pneumococcal vaccination and annual influenza vaccination[17]. Our survey results are in keeping with this recommendation. Most clinicians also advise varicella vaccination prior to corticosteroid therapy. No randomized controlled study of corticosteroid use in DMD patients has reported an increased risk of infection or instances of severe infection[1-4, 9,15].

Adolescent DMD patients have a higher incidence (44%) of malnutrition or obesity[63]. Dramatic increase in appetite associated with corticosteroid use results in rapid weight gain for many DMD patients, as defined by a 10-20% increase above baseline weight within 12 months[15]. Early dietary consultation has the potential to temper the steroid-associated weight gain; one randomized controlled trial with strict nutritional monitoring showed no significant weight gain in deflazacort-treated boys relative to placebo[4]. Many centres rely upon occupational therapy to screen for dysfunctional swallowing. Although occupational therapy is well suited in many instances to evaluate the mechanics of swallowing, dietician involvement may also help to eliminate or avoid certain types of foods in patients with early swallowing dysfunction.

CONCLUSIONS

Children with DMD are receiving relatively consistent care across Canada in multidisciplinary clinics. Duchenne muscular dystrophy management is largely in keeping with the recommendations with regard to corticosteroid use[16] and surveillance for cardiac and respiratory complications[17,18]. By describing the current clinical practice, existing scientific evidence and expert opinions, we hope to provide a comprehensive context for elevating the standard of practice in Canadian neuromuscular clinics and improve the care of DMD patients.

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