Neuromuscular Standards of Care

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Duchenne Muscular Dystrophy (DMD) / Becker Muscular Dystrophy (BMD)

- X-linked recessive disorder caused by a mutation in the dystrophin gene.
- 15.9 cases per 100,000 live male births in the USA.

https://geneticsupportfoundation.org/x-linked-inheritance
Figure 1. Nature Reviews Genetics 14, 373–378 (2013)
Diagnosis of DMD / BMD

- Muscle biopsy

Early DMD

- Dys immuno stain positive

2yo

- Dys immuno stain negative

10yo

- Dys immuno stain BMD

http://neuromuscular.wustl.edu/musdist/dmd.html
Diagnosis of DMD / BMD

- Genetic testing
  - 79 exons encode for the protein dystrophin
  - Most are intragenic out of frame deletions that lead to a severe reduction or absence of dystrophin
  - Other possibilities include: point mutations, in frame mutations, duplications.
Figure 2. Most commonly reported large mutations. Most commonly reported large deletions (recorded 100 times or more) (A) and large duplications (recorded ten times or more) (B) in the TREAT-NMD DMD Global database.
Initial Presentation of DMD

- Motor delays usually with onset around 2-5 years
  - Average age at diagnosis is 5 years of age.
- High creatine kinase levels
- Elevated liver function enzymes
- Known family history / in utero genetic testing
Duchenne Muscular Dystrophy

- Difficulty with getting up from seated or supine position – Gowers’ sign
- Difficulty with walking
- Difficulty with climbing stairs
- Most rely on wheelchairs by 7-13 years of age
- Average life expectancy is ~ 30 years

Childmuscleweakness.org
DMD Care Guidelines – New for 2018!

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management

David J Birnkrant, Katharine Bushby, Carla M Bann, Susan D Apkon, Angela Blackwell, David Brumbaugh, Laura E Case, Paula R Clemens, Stasia Hadjiyannakis, Shree Pandya, Natalie Street, Jean Tomezko, Kathyrn R Wagner, Leanne M Ward, David R Weber, for the DMD Care Considerations Working Group*

Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management

David J Birnkrant, Katharine Bushby, Carla M Bann, Benjamin A Alman, Susan D Apkon, Angela Blackwell, Laura E Case, Linda Cripe, Stasia Hadjiyannakis, Aaron K Olson, Daniel W Sheehan, Julie Bolen, David R Weber, Leanne M Ward, for the DMD Care Considerations Working Group*

Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan

David J Birnkrant, Katharine Bushby, Carla M Bann, Susan D Apkon, Angela Blackwell, Mary K Colvin, Linda Cripe, Adrianne R Herron, Annie Kennedy, Kathi Kinnett, James Naprawa, Garey Noritz, James Poysky, Natalie Street, Christina J Trout, David R Weber, Leanne M Ward, for the DMD Care Considerations Working Group*
Neuromuscular Management

- Lead the multidisciplinary clinic
- Advise on new therapies
- Provide patient and family support
- Genetic counseling
- Ensure immunization schedule is complete
- Discuss use of glucocorticoids → initiate → manage
- Refer female carrier to cardiologist
- Help navigate end of life care
Steroid therapy

- Usually started while a child plateaus in function
  - Dosing:
    - Prednisone 0.75mg/kg/day
      – if ambulant; 0.3mg/kg/day if non-ambulant
    - Deflazacort 0.9mg/kg/day – if ambulant; 0.5mg/kg/day if non-ambulant


J Pediatr 2017;182:296-303
Deflazacort vs. prednisone?

- RCT found an improvement in muscle strength at two years with deflazacort, with imprecise results on function at two years.
- Not enough data were available to adequately compare the efficacy of prednisone and deflazacort, although there is very low quality data favoring deflazacort for less weight gain.
- When compared, both prednisone and deflazacort are equivalent in improving motor function but there is insufficient evidence to establish a difference in effect on cardiac function. Prednisone is associated with increased weight gain in first years of treatment compared to increased risk of cataracts with deflazacort. Neurology 2016 Feb;86(5):465-72
- Slight differences in behavior have been noted in boys taking deflazacort as compared to prednisone. doi: 10.1371/currents.md.7628d9c014bfa29f821a5cd19723bbaa
  - Prednisone was described as having more externalized behavior – rule breaking / aggressive behavior
  - Deflazacort was described as having greater internalizing behavior – withdrawal and depression.

EXONDYS 51® is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
Antisense Oligonucleotide Therapy

https://vimeo.com/30272398
Research Trials

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Parent Project Muscular Dystrophy

Decode Duchenne
Free genetic testing, interpretation and counseling for individuals with Duchenne or Becker muscular dystrophy. Decode Duchenne is administered by DuchenneConnect and PPM and is funded by Sarepta Therapeutics and PTC Therapeutics.

NEWSFLASH

Updated Care Considerations for Duchenne
Microdystrophin Gene Therapy Trials
Understanding Clinical Trials Blog

Find a Clinical Trial
Easily search our family-friendly summaries of clinical trials and research studies.
Rehabilitation Management

- Provide comprehensive multidisciplinary assessments every 6 months
- Provide direct treatment by PT and OT
- Speech therapist if needed
- Aquatherapy
- Mobility support
  - Hoyer
  - Hospital bed
  - Walker
  - Wheelchair
Endocrine management

- Measure height every 6 months
  - Risk of decreased linear growth with DMD and while on steroids
- Assess non-standing growth every 6 months
- Assess pubertal status every 6 months starting by age 9 years
  - Risk of delayed puberty while on steroids
- Provide family education on stress dose steroid prescription if on glucocorticoids if on prolonged therapy
Gastrointestinal management

- Assess swallow dysfunction, constipation, gastroesophageal reflux, and gastroparesis every 6 months
- Initiate annual discussion of gastrostomy tube as part of usual care.
Nutritional management

- Provide annual assessment of vitamin D 25-OH and calcium intake.
- Include assessment by registered dietitian nutritionist at clinic visits (every 6 months): initiate obesity prevention strategies; monitor for overweight and underweight, especially during critical transition periods.
Panel 3: General nutritional plan

This general nutritional plan, which is created from recommendations for the general healthy population and is not specific to patients with DMD, provides methods to assess energy, protein, fluid, and micronutrient requirements on the basis of dietary reference intakes. To meet the body’s daily nutritional needs while minimising risk of chronic disease, adults should consume 45–65% of their total calories from carbohydrates, 20–35% from fat, and 10–35% from protein. The acceptable ranges for children are similar to those for adults, except that infants and younger children need a somewhat higher proportion of fat in their diets.110

Overall caloric needs

Overall caloric needs are based on total energy expenditure, which is equal to resting energy expenditure (REE) multiplied by the physical activity factor.

Indirect calorimetry provides the most accurate measure of REE, but REE can also be estimated in steroid-treated ambulatory boys with DMD (aged 10–17 years) by the Schofield weight equation (REE [kilocalories] = [17.7 × weight in kg + 657] × 4.182/1000).111 Because of the decline in physical activity that accompanies a loss of ambulation, calorie needs can decrease substantially, and REE might be even lower than the REE before the loss-of-ambulation phase.

Physical activity factors for boys aged 3–18 years are sedentary (1.00), low active (1.13), active (1.26), and very active (1.42).

The calculated energy or caloric intake will need to be decreased if initial energy or caloric prescription does not result in weight maintenance or weight loss. If the goal is weight increase, the calculated energy or caloric intake will need to be increased.

Protein

Recommended dietary allowance for protein differs for boys and men according to age: a dietary allowance of 0.95 g/kg bodyweight per day is recommended for children aged 4–13 years; 0.85 g/kg per day is recommended for those aged 14–18 years; and 0.80 g/kg per day is recommended for men aged 19 years or older.

Fluids

Recommended fluid intake (total beverages, including drinking water) is based on weight or age.

Based on weight, the Holliday–Segar maintenance fluid method112 recommends 100 mL/kg bodyweight for children who weigh 1–10 kg; 1000 mL + 50 mL for each kg over 10 kg for children who weigh 10–20 kg; and 1500 mL + 20 mL for each kg over 20 kg for children and adults who weigh more than 20 kg.

Based on age, the daily dietary reference intake values for fluids are 1.2 L (approximately 5 cups) for boys and girls aged 4–8 years; 1.8 L (approximately 8 cups) for boys aged 9–13 years; 2.6 L (approximately 11 cups) for boys aged 14–18 years; and 3.0 L (approximately 13 cups) for men aged 19 years or older.

Micronutrients

Recommended dietary allowance for age113 should be followed, except in the case of vitamin D deficiency, which is defined as 25-hydroxyvitamin D of less than 30.0 ng/mL. A multivitamin or mineral supplement is necessary if calorie intake is low.
Respiratory Management

- Complications are a major cause of morbidity and mortality
  - Mucus plugging
  - Atelectasis
  - Pneumonia
  - Respiratory muscle fatigue
  - Respiratory failure

- Pulmonary disease
  - Restrictive lung disease
    - Main contributor is scoliosis
  - Sleep hypoventilation
    - Obstructive sleep apnea; treat with night-time non-invasive ventilation / BiPAP
Respiratory management

- Pulmonary function testing starting around 5-6 years of age; yearly at least. Mainly monitoring forced vital capacity (FVC)
- Ensure immunizations are up to date: pneumococcal vaccines and yearly influenza vaccine.
- Cough assist when necessary
  - Difficulty clearing secretions or FVC <50% predicted or MEP <60cm H2O
- Nocturnal/day time ventilation when necessary.
  - If sleep study abnormal, FVC <50% predicted, MIP <60cm, or awake baseline O2 <95% or pCO2 >45mm Hg
Respiratory management

- Whether individuals with DMD should be ventilated via tracheostomy or non-invasively is controversial.

- Some centers use time on the ventilator as an indication for tracheostomy, but clinical experience supports the use of non-invasive ventilation for up to 24hrs/day.
  - Breathebb.com
  - Breathenvs.com

- Potential indications for tracheostomy include
  - Patient preference
  - Inability to use non-invasive ventilation
  - Three failed extubation attempts during critical illness despite optimum use of non-invasive ventilation and mechanical coughing
  - Failure of non-invasive methods of cough assistance to prevent aspiration of secretions into the lungs due to weak bulbar muscles.
Due to concerns for cardiomyopathy, consult cardiologist; assess with electrocardiogram and echocardiogram or cardiac MRI
Assess cardiac function annually
Initiate ACE inhibitors or angiotensin receptor blockers by age 10.
Assess cardiac function at least annually, more often if symptoms or abnormal imaging are present; monitor for rhythm abnormalities.
Carriers should be assessed at least every 5 years
Bone health

- Assess with lateral spine x-rays every 1-2 years; if not on glucocorticoids then every 2-3 years.
- Refer to bone health expert at the earliest sign of fracture.
Orthopedic management

- Assess range of motion and spinal curvature at least every 6 months.
- Consider Schroth physical therapy.
- Refer for orthopedic surgery if needed; surgery is considered if curve progresses past 20 degrees.
- Refer for surgery on foot and achilles tendon to improve gait in selected situations.
- Consider intervention for foot position for wheelchair positioning
Psychosocial management

- Assess mental health of patient and family at every visit and provide ongoing support.
- Provide neuropsychological evaluation / intervention for learning, emotional and behavioral problems.
  - Pervasive developmental disorder
  - ADD/ADHD
  - OCD
  - Social isolation
  - Depression / anxiety
- Assess educational needs and available resources; assess vocational support needs for adults.
- Promote age appropriate independence and social development.
Transitions

- Engage in optimistic discussions about the future, expecting life into adulthood.
- Foster goal setting and future expectations for adult life, assess readiness for transition by age 12 years.
- Initiate transition planning for health care.
- Provide transition support and anticipatory guidance about health changes.
Thank you!

My patients!