

Duchenne Muscular Dystrophy: Neuromuscular Care Considerations

PPMD Tour

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David Dredge, MD

Co-Director, MGH Pediatric Neuromuscular clinic

Objectives

- **Brief introduction of DMD**
- **Steroid therapy**
- **Emergency management**

Disclosures

- Site director, PPMD Certified Care Center
- Site director, MDA Care Center
- Co-investigator, Pfizer study (closed)

DMD overview

- Relatively common genetic disorder (1/3000-5000 live-born boys)
- Presents with weakness usually by age 3-5
- Progressive weakness of skeletal and heart muscles
- Most current treatments only slow progression
- There is currently no cure (but some exciting treatments on the horizon)

Making the Diagnosis

- Most boys present with developmental delays or weakness early in life
- Common early symptoms:
 - Abnormal gait
 - Large calf muscles
 - Fatigue
 - Trouble with stairs
 - Frequent falls
 - Delayed motor milestones
 - Low muscle tone
 - Toe walking
 - Loss of motor milestones
 - Learning and behavior issues
 - Poor weight gain

Diagnosis

- We recommend that all boys with developmental delay have a creatine kinase (CK) level checked
 - This muscle enzyme is typically very elevated (>10,000 units) in DMD patients even early in life
- Some cases are determined before symptoms develop
 - Lab studies done for other reasons (liver function tests) can be elevated
 - Genetic testing for developmental delay can pick up changes in the X chromosome
 - Newborn screening is coming soon

Diagnosis

- If elevated CK level or strong suspicion, genetic testing
 - Deletion and duplication analysis
 - If normal, gene sequencing
- Determining the specific mutation with genetic testing is very important!
 - Some new treatments are mutation-dependent

Treatment

- **Physical therapy**
- **Corticosteroids**
- **Many other treatments are in trials currently**

Steroids: The good, the bad, the confusing

- **The good:**
 - Corticosteroids (prednisone, deflazacort) have been demonstrated in multiple studies to:
 - Delay the age at which boys require a wheelchair by 1-3 years
 - Preserve upper extremity function in non-ambulatory boys
 - Preserve respiratory function
 - Slow development of scoliosis and its complications

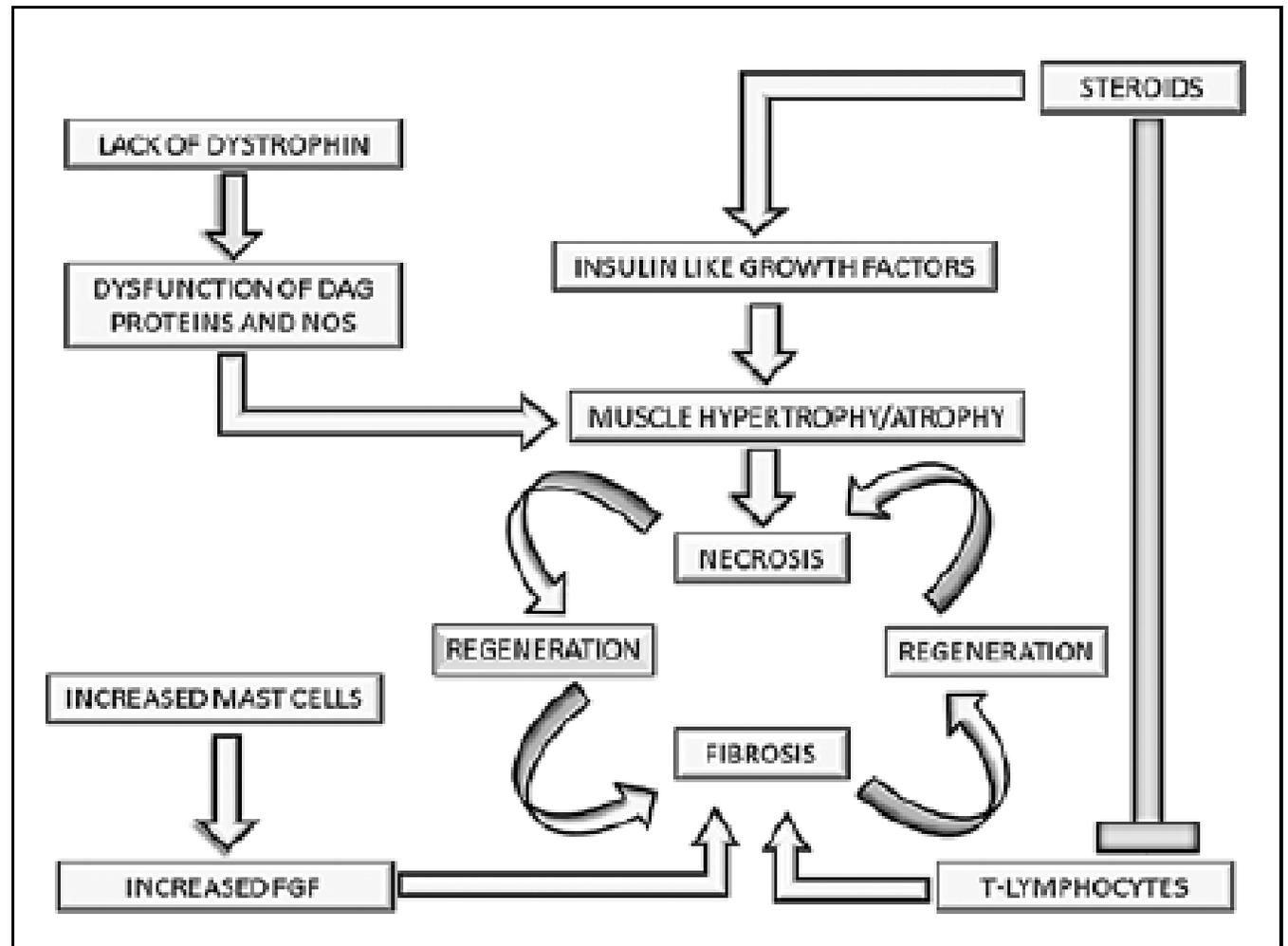
Not those
steroids



Steroids: The good, the bad, the confusing

- **How corticosteroids work in DMD**
 - Slow down muscle degeneration
 - Reduce T-cells (immune cells)
 - Reduce inflammation (reduced NF-kB, other cytokines)
 - Stimulate growth of new muscle cells
 - Increase utrophin and other proteins associated with the muscle cell membranes

Steroid mechanism



Steroids: The good, the bad, the confusing

■ The bad:

■ Common steroid related side effects

- Increased appetite and weight gain
- Irritability
- Facial swelling
- Decreased bone mineral density
- Stomach upset, reflux
- Headaches
- Acne
- Increased hair
- Insomnia
- Delayed puberty
- Decreased linear growth

■ Rare side effects

- Cataracts
- Insulin resistance (diabetes-like state)
- High blood pressure
- Adrenal insufficiency

Steroids: The good, the bad, the confusing

- The confusing-- there is no general consensus regarding:
 - What age to start
 - Which steroid is best (prednisone vs. deflazacort)
 - What dose and dosing schedule
 - Duration of therapy

Evidence-based medicine

- The gold standard of medical evidence is randomized, double-blinded, placebo-controlled trials
 - Require high numbers of patients to be most useful
- RCTs are difficult to carry out in rare diseases
- Very few RCTs in DMD

When to start?

- Early treatment, before significant loss of function and muscle is recommended
- Historically patients were started around 5 years old
- There is some data that patients started at a younger age (2-4 years) had slower progression of weakness
- However, early initiation can lead to reduced linear growth and delayed puberty
 - Balance longer exposure to side effects with potentially greater benefit

When to start?

- **Need to complete vaccines prior to starting steroids**
 - Unable to mount the appropriate immune response to the vaccine
 - Need to wait 2 months after vaccine to start treatment
- **Treat pre-symptomatic patients?**
- **Current recommendation is “before significant physical decline”**

Which steroid?

- Prednisone has been around for decades
- Deflazacort was only approved by the FDA in 2017
 - Available in Canada and Europe for decades
- The two medications share the same method of action

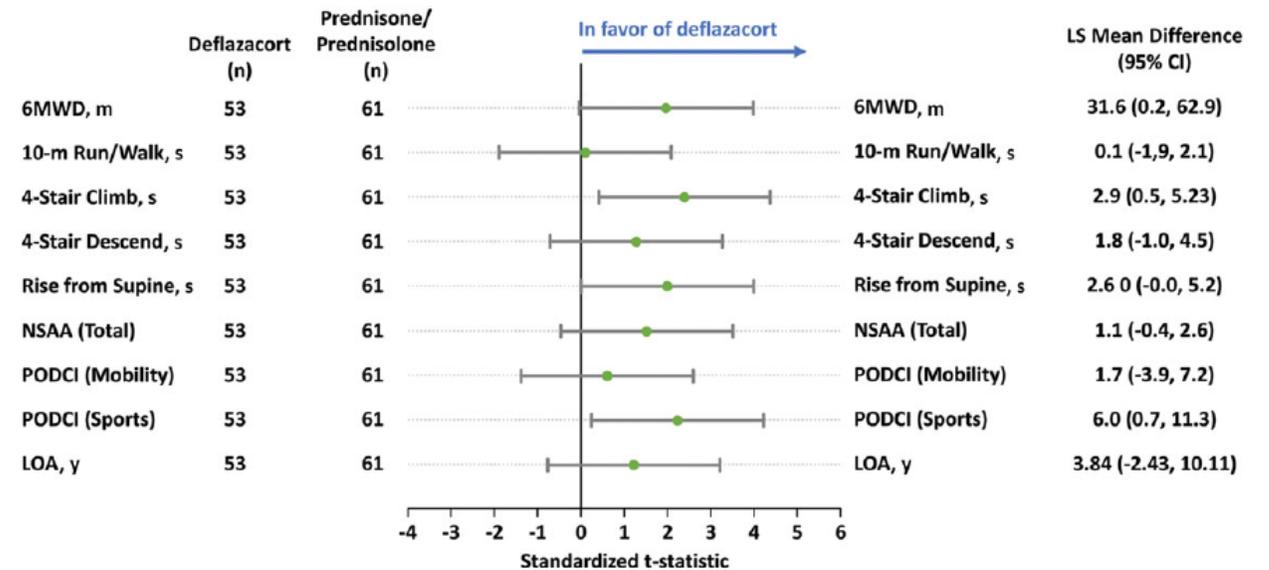
Which Steroid?

- Several studies in the last 10 years have compared the 2 drugs
 - Only 1 RCT
- Most have demonstrated equivalent efficacy
- Deflazacort less likely to cause weight gain
- Deflazacort more likely to cause cataracts (asymptomatic)
- Other side effects essentially equivalent
 - Behavioral

Which steroid?

- **ACT-DMD study**
 - Placebo controlled trial of ataluren
 - All boys (114) in the placebo group were on steroids
 - Data on steroid therapy was analyzed post-hoc
- **2018 paper demonstrated:**
 - Deflazacort better than prednisone in several standard measures

Deflazacort vs. Prednisone



Deflazacort vs. Prednisone

TEAE, <i>n</i> (%)	Deflazacort (<i>n</i> = 53)	Prednisone/Prednisolone (<i>n</i> = 62)
Pain in abdomen (including upper abdomen)	0 (0)	18 (29)
Nasopharyngitis	6 (11)	17 (27)
Headache	10 (19)	11 (18)
Vomiting	10 (19)	11 (18)
Fall	8 (15)	12 (19)
Pain in extremity	6 (11)	8 (13)
Cough	5 (9)	8 (13)
Pyrexia	4 (8)	8 (13)
Constipation	4 (8)	6 (10)
Back pain	2 (4)	6 (10)
Upper respiratory tract infection	0 (0)	6 (10)
Diarrhea	5 (9)	5 (8)
Ligament sprain	3 (6)	4 (6)
Nausea	3 (6)	4 (6)
Oropharyngeal pain	2 (4)	4 (6)

Deflazacort vs. Prednisone

Measurement	Deflazacort (<i>n</i> = 53)	Prednisone/prednisolone (<i>n</i> = 62)
Weight, kg		
<i>n</i>	50	59
Mean change (SD)	3.9 (2.6)	4.6 (3.2)
95% CL	3.2, 4.6	3.8, 5.4
Median	3.8	3.8
Height, cm		
<i>n</i>	50	59
Mean change (SD)	3.2 (2.0)	3.9 (1.9)
95% CL	2.7, 3.8	3.4, 4.4
Median	3.0	4.0
BMI, kg/m ³		
<i>n</i>	50	59
Mean change (SD)	1.3 (1.3)	1.6 (1.5)
95% CL	1.0, 1.7	1.2, 1.9
Median	1.3	1.4

Deflazacort vs. Prednisone

- 3 severe adverse effects in deflazacort (myocarditis, abnormal liver function tests, lower limb fracture)
- 1 severe adverse effect in prednisone group (gastroenteritis)

Deflazacort vs. Prednisone

- So why not just use deflazacort?
- In 2017 Emflaza was FDA approved for DMD
 - Orphan drug status
 - Cost per year went from about \$1000/year if imported from the UK/Canada to \$65,000/year
 - Most insurances are covering Emflaza, whereas families payed out of pocket for imported deflazacort
 - Now technically illegal to import it

Which dosing regimen?

- The standard recommended doses are 0.75 mg/kg/day of prednisone or 0.9 mg/kg/day of deflazacort
 - Dose reduction is often required due to side effects
 - 0.3 mg/kg/day of prednisone—fewer AEs but may not be as effective
- Weekend only, 5 mg/kg x 2 days
 - Equivalent efficacy and side effects
- Every other day
 - Not enough data
- 10 days on, 10 days off
 - Not enough data
- Not much data on alternative dose schedules of deflazacort

Emergency care/stress dose steroids

- Long term use of exogenous steroids may suppress the function of the adrenal gland
- The adrenal gland secretes cortisol, an important hormone secreted in times of stress
 - Infection
 - Illness
 - Dehydration
 - Surgery
 - Trauma
 - Missed doses of meds

Adrenal insufficiency

- If adrenal function is suppressed, the body cannot mount the usual stress response
- Adrenal insufficiency can lead to adrenal crisis
 - Abdominal pain
 - Confusion
 - Dizziness
 - Headache
 - Fatigue
 - Low blood pressure
 - Nausea
 - Weakness
 - Changes in breathing and heart rate
 - Coma
- If untreated, adrenal crisis can be fatal

Adrenal suppression

- Not all patients on steroids have adrenal suppression
- Depends on dose and duration of therapy

Prednisone dose Equivalents/day - Adults	Prednisone Dose Equivalents/Day - Pediatric	Suppression of HPA axis?
5mg/day or less	3 mg/m ² /day or less	Usually not suppressed.
5 – 20 mg/day	3-12 mg/m ² /day	Possibly suppressed. ACTH stimulation test recommended or give supplemental dose.
20 mg/day for >10 days or more	12 mg/m ² /day of prednisone for > 10 days or more	Suppressed. Give supplemental dose.

Adrenal insufficiency treatment

- If any triggers for adrenal crisis are present, treat with stress-dose hydrocortisone

Medical/Surgical Stress	Corticosteroid Dosage DOS*	Postoperative Taper Regimen
Minor (local anesthesia, < 1 hour) (e.g. inguinal hernia, single tooth extraction, colonoscopy), mild febrile illness, mild, nausea/vomiting, mild diarrhea)	25mg or 30-50 mg/m ² po (if able to take po) or IV hydrocortisone (HC) or equivalent	None Resume maintenance physiologic dose of hydrocortisone when illness, pain or fever subsides
Moderate (e.g. multiple teeth extraction, fracture, pneumonia)	50mg or 50-75 mg/m ² IV hydrocortisone or equivalent	25 mg Q 8 or 50-75 mg/m ² /day ÷ q 6 hours X 24 hour. Taper to baseline over 1-2 days.
Major (e.g. Septic shock, multiple trauma/fractures or severe burns, severe systemic infections, major surgery, pancreatitis, orthopedic surgery including open reduction, spinal fusion, etc.)	100mg or 100 mg/m ² /dose IV hydrocortisone or equivalent	50 mg IV Q 8 or 100 mg/m ² /day ÷ q 6 hours X 24-48hours. Taper to baseline over 1-3 days (continue stress dose if the physical stress (fever or pain) continues).

Conclusion

- The benefits of steroid therapy are well-established
- All boys should be on a steroid
- Start treatment before substantial physical decline (3-5 years)
- Side effects are problematic but can be mitigated by changes in dose or treatment regimen
- No consensus on which steroid is best, but recent data suggests deflazacort may be more effective with fewer side effects
- Patients on long-term steroid therapy require stress-dose steroids if ill or having surgery