# Corticosteroid Treatment of Duchenne Muscular Dystrophy (DMD)

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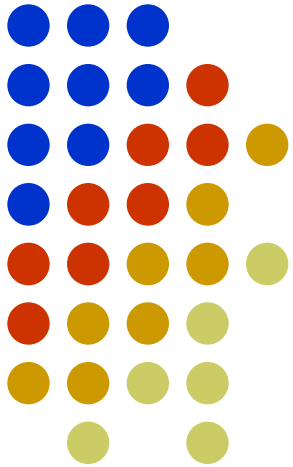
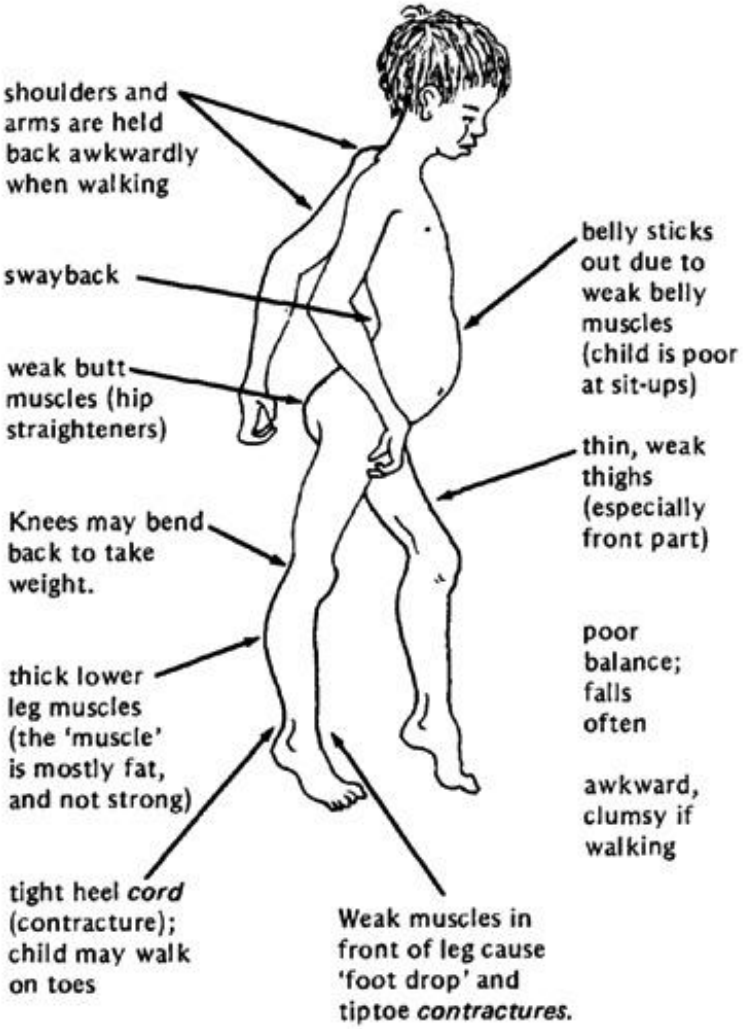
# Introduction

# DMD

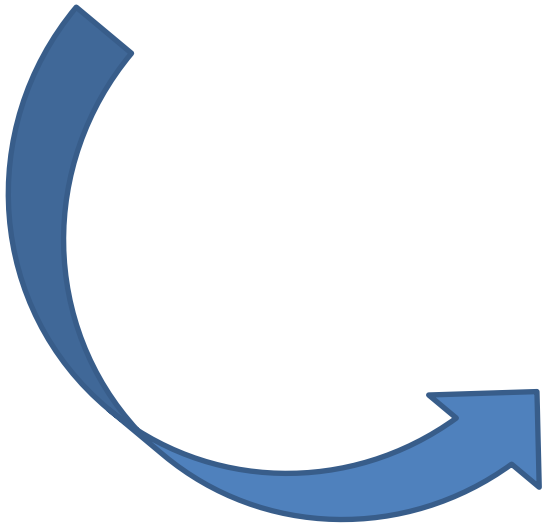
- Is an X-linked, recessive disorder with onset before age five years.
- Is the most common and severe form of childhood muscular dystrophy.
- A absence or marked deficiency of dystrophin, the protein membrane that is part of the dystrophin-glycoprotein complex.
- Patients develop neck flexor, anterior abdominal, hip and shoulder girdle muscle weakness in early childhood.
- Loss of ambulation between ages 7 and 12 years.

# Clinical Picture



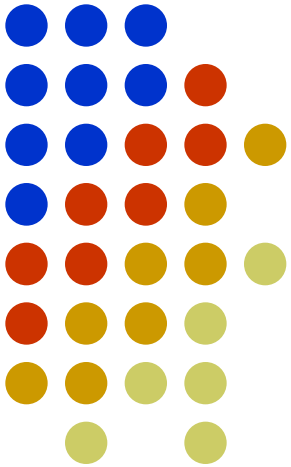
# Treatment?

- Physiotherapy
- Medication?



**Corticosteroides ?**

# Role of Corticosteroides

# In the past

## History of Corticosteroid Use for DMD

**PREDNISONE IN DUCHENNE MUSCULAR DYSTROPHY**

D. B. DRACHMAN K. V. TOYKA
E. MYER

*Neuromuscular Unit, Department of Neurology, Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205, U.S.A.*

***Summary*** Fourteen patients with typical Duchenne muscular dystrophy were treated with prednisone for up to 28 months. Thirteen patients showed improvement in motor power and muscular activities while on prednisone. In eight of these, the improvement has been maintained for up to 28 months, while in five others deterioration has occurred while on medication. Creatine-phosphokinase levels did not correlate with the clinical status of the patients; in nine patients they fell by more than 45% at first, but subsequently returned to pre-treatment levels. Prednisone may provide a useful palliative treatment for some patients with the Duchenne form of dystrophy.

Lancet, Dec (1974) p. 1409

SUMMARY OF PREDNISONE TRIAL IN DUCHENNE MUSCULAR DYSTROPHY

| Patient | Initial age | Duration of treatment (mo.) | Improvement of | | Late worsening† | Side-effects‡ | % fall in C.P.K. at 3–10 wk. |
|---|---|---|---|---|---|---|---|
| | | | Activities* | Muscle strength | | | |
| 1 | 6 yr. | 28 | + + | + + | ± | Slight hyperactivity | 6 |
| 2 | 4 yr. 6 mo. | 28 | + + | + | 0 | Slight hyperactivity | 50 |
| 3 | 8 yr. 6 mo. | 12 | + | + | + | 0 | 72 |
| 4 | 9 yr. 3 mo. | 28 | + + | + + | 0 | 0 | 60 |
| 5 | 6 yr. | 12 | + | Not testable | 0 | Hyperactivity | 61 |
| 6 | 8 yr. 6 mo. | 12 | + + | + + | + | Gastritis, weight gain | 66 |
| 7 | 8 yr. 8 mo. | 7 | + | Not evaluated | 0 | 0 | 3 |
| 8 | 10 yr. | 3 wks. | 0 | 0 | 0 | 0 | .. |
| 9 | 10 yr. 6 mo. | 3·5 | + | + + | 0 | 0 | 45 |
| 10 | 3 yr. 6 mo. | 28 | + + | + + | 0 | 0 | 16 |
| 11 | 3 yr. | 28 | + + | + (? reliable) | 0 | 0 | 52 |
| 12 | 6 yr. | 28 | + + | + | + | 0 | 53 |
| 13 | 10 yr. 2 mo. | 5 | + + | + + | 0 | 0 | +30 |
| 14 | 8 yr. | 28 | + | + + | ± | 0 | 48 |

* Walking, running, climbing stairs, and so on. † While on prednisone. ‡ Other than cushingoid facies.
0 = No quantitative change.
+ = Consistent improvement in dynamometry, or M.R.C. rating (less than 1 grade).
+ + = Improvement of 1 M.R.C. grade in 2 major muscle groups.

# American Academy of Neurology, 2005

## Practice Parameter: Corticosteroid treatment of Duchenne dystrophy

**Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society**

R.T. Moxley III, MD; S. Ashwal, MD; S. Pandya, MS, PT; A. Connolly, MD; J. Florence, MHS, PT; K. Mathews, MD; L. Baumbach, MD; C. McDonald, MD; M. Sussman, MD; and C. Wade, PhD, PT, RN

NEUROLOGY 2005;64:13–20

- "Conclusions: Prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with Duchenne dystrophy and should be offered…as treatment."
- "Deflazacort…can also be used for the treatment of Duchenne dystrophy in countries in which it is available."

# How They work?

- Precise mechanism unknown
- Many theories:
  - Anti-inflammatory/immunosuppressive effect
  - Inhibit muscle protein breakdown
  - Stimulation of muscle precursor cell proliferation
  - Stabilization of muscle fiber membranes
  - Increased muscle repair
  - Reduced muscle cell calcium
  - Up-regulation of utrophin

# How we use

## Practical Use of Corticosteroids for DMD

- When to start?
  - No clear guidelines
  - 3 phases of motor function:

| Age <2 years | Age 2–5 years | Age ≥6 years |
|---|---|---|
| Improving (typical): GC initiation not recommended<br>Plateau (uncommon): monitor closely<br>Decline (atypical): consider alternative diagnoses/concomitant pathology | Improving: GC initiation not recommended<br>Plateau: GC initiation recommended<br>Decline: GC initiation highly recommended | Improving (uncommon): consider BMD<br>Plateau: GC initiation highly recommended<br>Decline: GC initiation highly recommended<br>Non-ambulatory: refer to text |

- Consider age, function (improving, plateau, declining), pre-existing risk factors, physician relationship with family
- Ensure immunisation schedule is complete before initiating GCs

Bushby et al, 2010

  - Generally: target plateau phase of motor development (usually 4-8 years old)

# Other way

## Practical Use of Corticosteroids for DMD

- Other dosing regimens
  - Less evidence
  - Goal: reduced side effects
  - Alternate day: less effective than daily
  - 10 days on, 10-20 days off: least effective, best tolerated
  - High-dose weekend prednisone
    - 10 mg/kg over 2 days
    - Similar benefit after 12 months w/ daily dosing

# Evidence for Prednision

- Seven class I studies have demonstrated that prednisone is beneficial in DMD.
- 0.75 mg/kg/d is optimal as an initial dosage for boys between 5 to 15 years of age.
- Outcomes measured include muscle strength, 24-hour urinary excretion of creatinine, muscle function, and pulmonary function.

# Evidence for Prednision

- Prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with DMD and should be offered (at a dose of 0.75 mg/kg/d) as treatment**.** (**Level A**) Maintaining a dosage of 0.75 mg/kg/d is optimal; but, if side effects require a decrease in prednisone, tapering to dosages as low as 0.3 mg/kg/d gives less robust but significant improvement.

- Benefits and side effects of corticosteroid therapy need to be monitored. Timed function tests, pulmonary function tests, and age at loss of independent ambulation are useful to assess benefits. An offer of treatment with corticosteroids should include a balanced discussion of potential risks. (**Level A**)

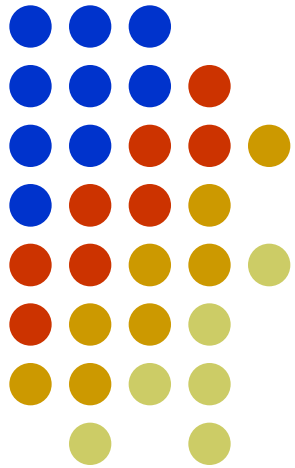
# Side-Effects

- Potential side effects of corticosteroid therapy need to be assessed: (**Level A**)
  - Weight gain
  - Cushingoid appearance
  - Cataracts
  - Short stature
  - Acne
  - Excessive hair growth
  - Gastrointestinal symptoms
  - Behavioral changes
- If excessive weight gain occurs (>20% over estimated normal weight for height over a 12 month period), based on available data, it is recommended that the dosage of prednisone be decreased (to 0.5 mg/kg/d with a further decrease after 3-4 months to 0.3 mg/kg/d if excessive weight gain continues)**.** (**Level A**)

# Evidence for Deflazacort

Deflazacort (0.9 mg/kg/d) can also be used for the treatment of DMD in countries in which it is available **(Level A).** Patients should be monitored for asymptomatic cataracts as well as weight gain during treatment with deflazacort.

# Continue to Research

# Future Research

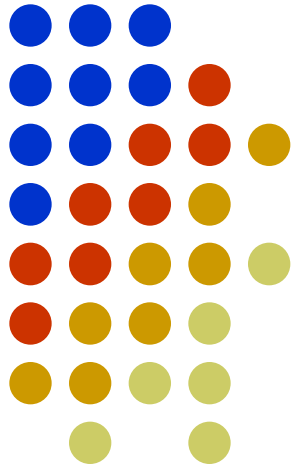
- Double blind, randomized, controlled studies are needed to compare daily treatment with prednisone to other treatment regimens, such as:
  a) higher dose alternate day treatment (5 mg/kg every other day)
  b) intermittent treatment (0.75 mg/kg/d for 10 days – stop for 10 days – repeat cycle)
  c) high dose pulses on weekends (5mg/kg on Friday and Saturday) and
  d) deflazacort (0.9 mg/kg/d).

- The goal of these studies is to establish more clearly the optimal dose, optimal age to initiate treatment, and optimal dose schedule to improve function with the least possible side effects.

# New Developments and Future Directions


- New steroid-like medication
- Ages 4-7, not on steroids
- Goal: retain beneficial aspects of corticosteroids, decrease/eliminate adverse effects

# Take home messages

Duchenne

- X-linked
- deficiency of dystrophin
- No specific Medication


Corticoides treatment

- Class 1, Level A
- Prednison and Deflazacort
- Side effects

Future Research

- Control Side effects
- New steroides

# Thank you!