New (and Old) Corticosteroid news

Anne M. Connolly, MD

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Amsterdam

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Amsterdam, September 7th, 2018

- Disclosures
- Advisory Boards
  - Sarepta, Ionis, Roche, Genzyme, AveXis
- Data Management Safety Board
  - Catabasis
- Site PI
  - Sarepta, Biogen, Roche, Avexis, Italafarmaco,
  - NS Pharma

Anne M. Connolly, MD
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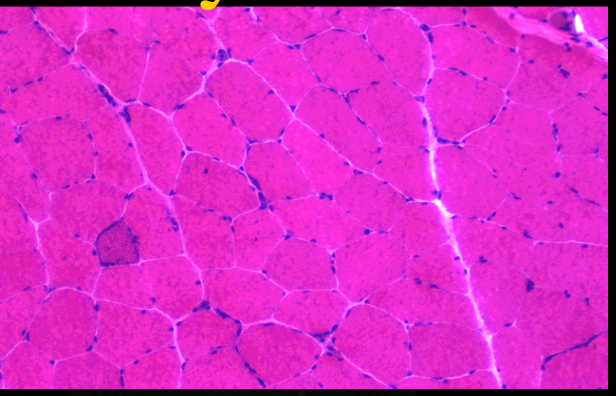
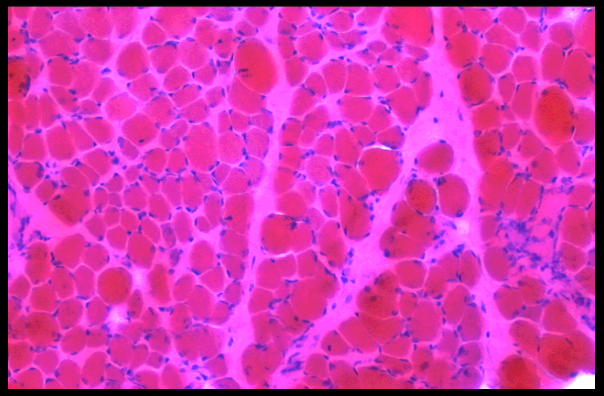
DMD: Progression over 8 years

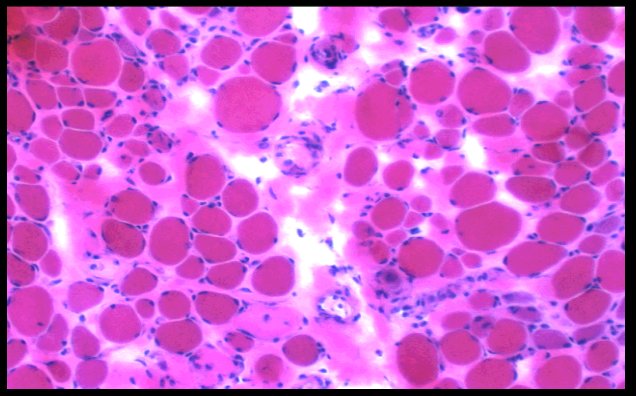
2 years

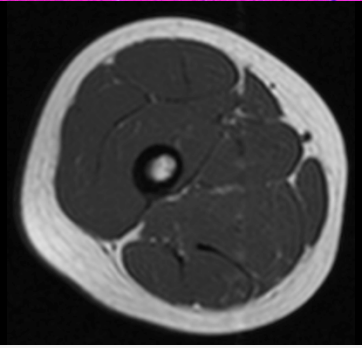
5 years

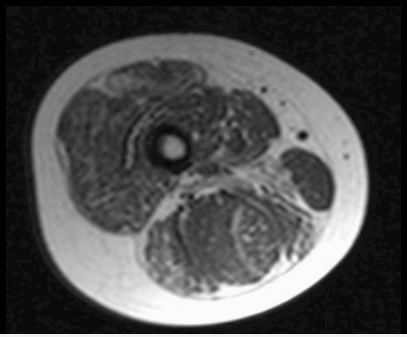
10 years

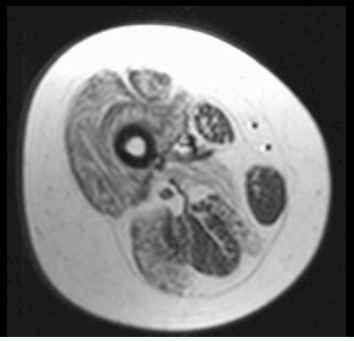


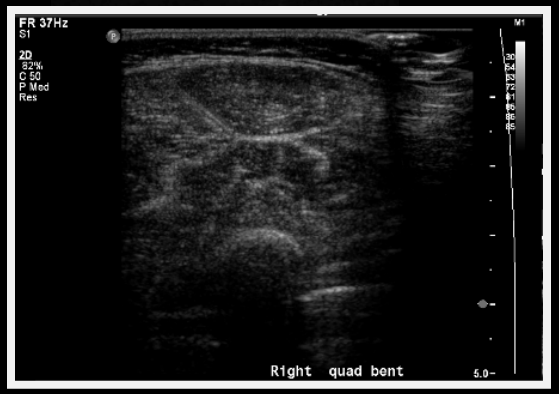


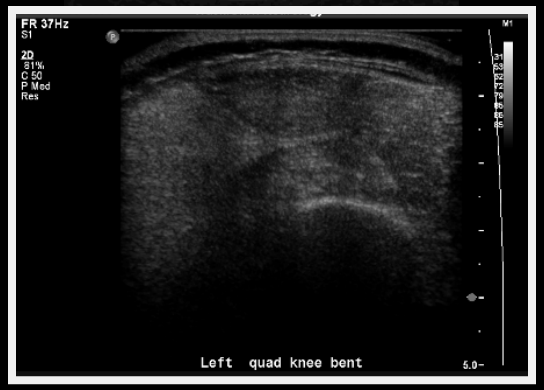












Why (Not) Corticosteroids?

…or "How do I (not) love thee, let me count the ways"…

- Weight gain
- Cushingoid features
- Insulin resistance/diabetes
- Behavior
- Osteopenia, fractures
- Delayed puberty
- Hirsutism
- Growth stunting
- Cataracts
- Adrenal insufficiency/risk for adrenal crisis

Corticosteroids; early years

1974- Pilot (Drachman, Toyka, Myer-Lancet)

- 1980-91's: ClDD Group
- Daily prednisone (0.75mg/kg/day) improves strength

Prednisone in Duchenne Dystrophy

A Randomized, Controlled Trial Defining the Time Course and Dose Response

Robert C. Griggs, MD; Richard T. Moxley III, MD; Jerry R. Mendell, MD; Gerald M. Fenichel, MD; Michael H. Brooke, MD; Alan Pestronk, MD; J. Philip Miller

Arch Neurol. 1991;48(4):383-388. doi:10.1001/archneur.1991.00530160047012. Text Size: A A

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Twice Weekly high dose oral prednisone (search for alternative)

- Background
  - From 1991-1999 I succeeded in getting virtually every boy's family to TRY daily corticosteroids (0.75mg/kg/day)
  - Side effects: obesity, linear growth slowing/arrest such that more than <u>50% would discontinue therapy</u>

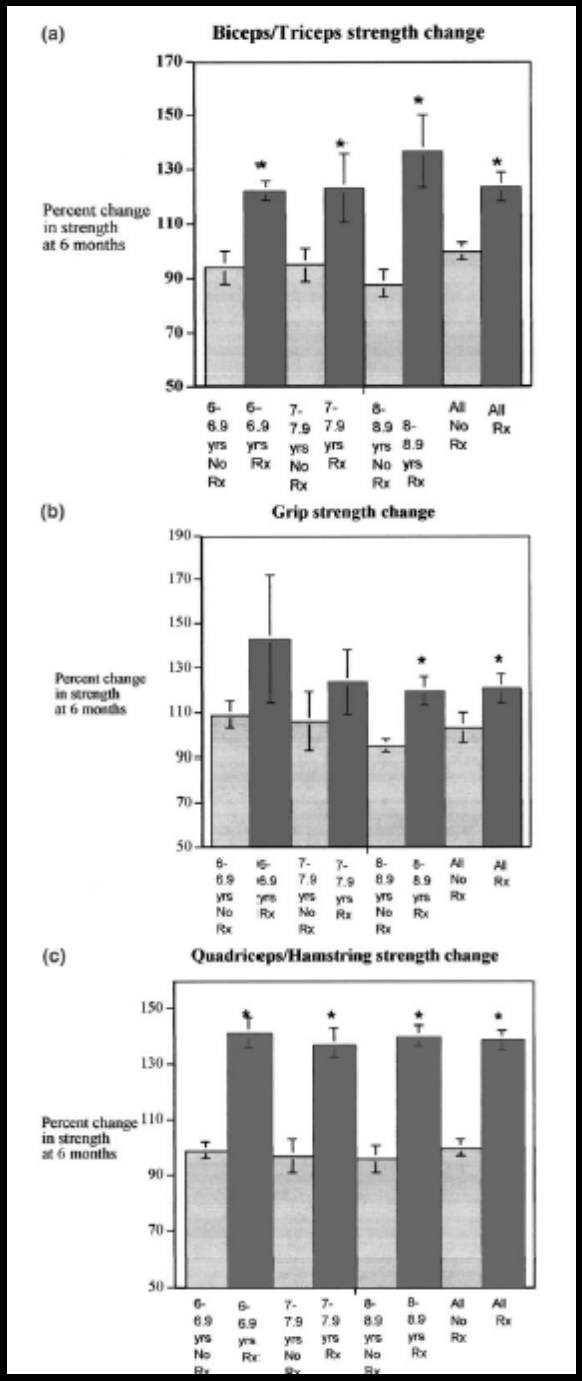
- Methods
  - 10mg/kg/ week- prednisone in two daily doses
  - Exam, height, weight, quantitative strength with hand held manometer
- 20 consecutive treated boys with DMD

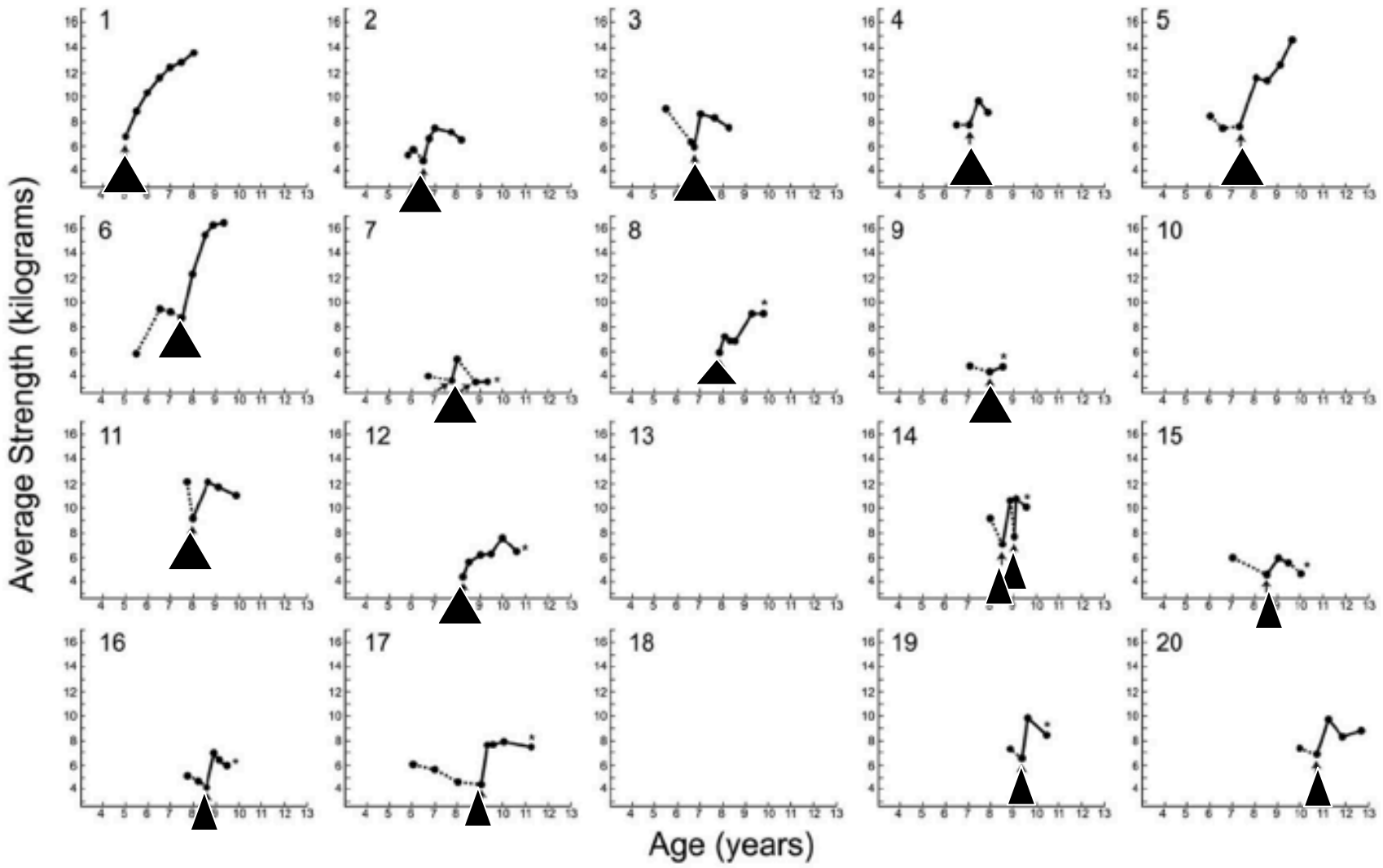
Twice weekly corticosteroids were effective in Pilot study of boys with DMD (age 8 +/-1.2 years) over one year.

- P=.001 for upper extremity
- p=.002 for grip
- p=<.0001 for lower extremity

- Linear growth was maintained
- Obesity rates were the same as untreated historical controls.
- Cushingnoid features including hirsutism, acne, stria, and hypertension did not occur. No cataracts developed.
- 16 treated >1 year; 15/16 remained stronger than baseline

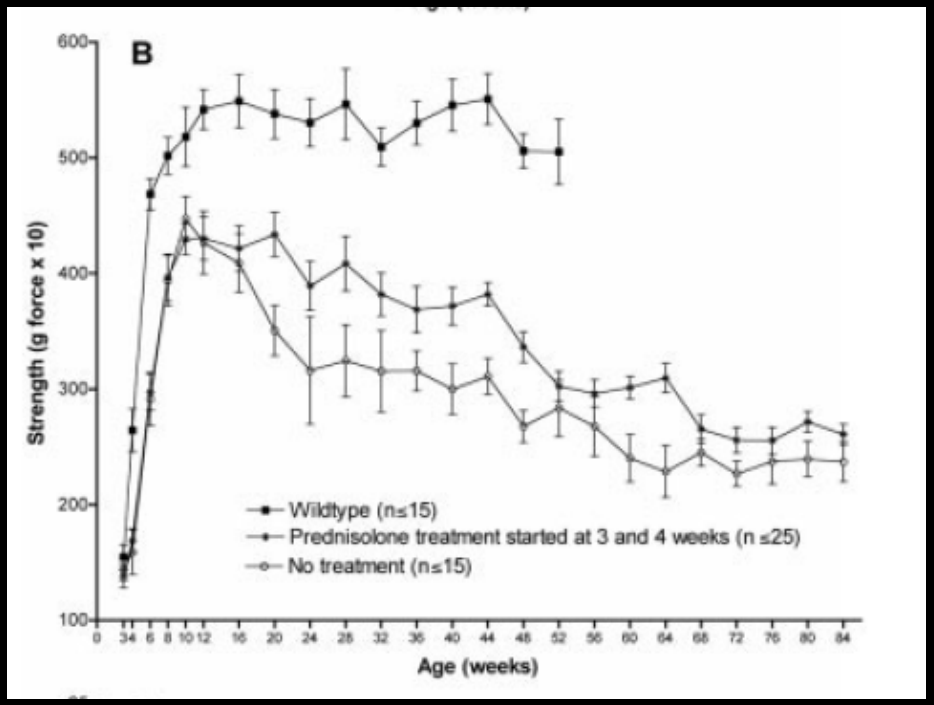
2002: Connolly, Schierbecker, Renne, Florence, Neuromuscular disorders



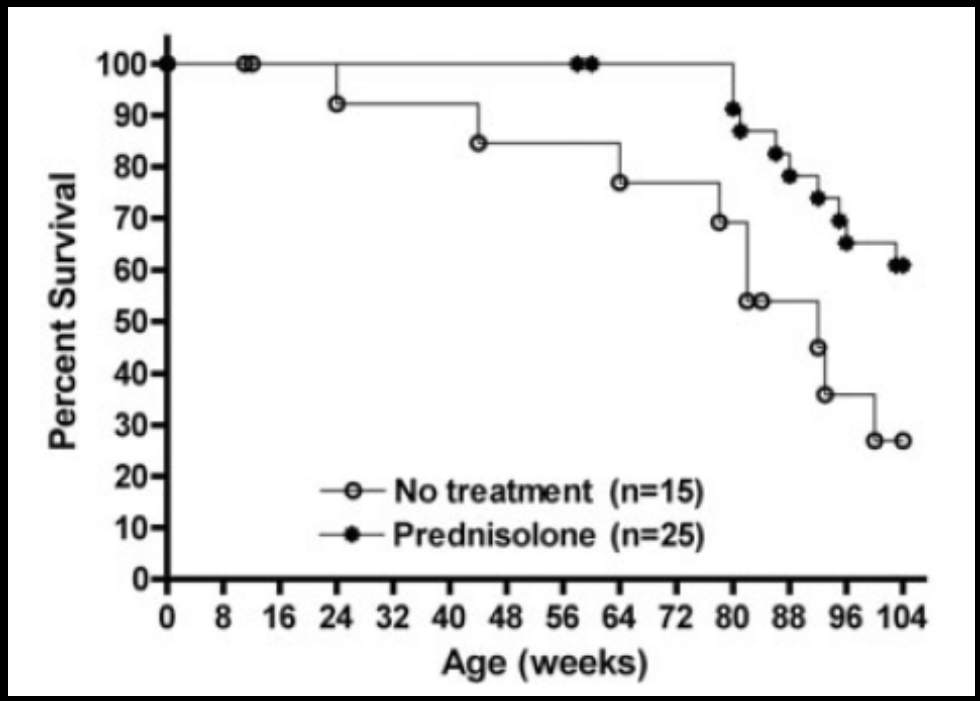


- 2002: Connolly, Schierbecker, Renne, Florence, Neuromuscular disorders

mdx Mouse: Twice weekly oral prednisolone improves strength and survival



Grip Strength



Survival

2007: Muscle and Nerve: Keeling Golumbek, Streif, and Connolly

Randomized, blinded trial of twice weekly vs. daily prednisone in Boys with DMD

- 64 boys
  - 4 to 10 yrs; daily (0.75mg/kg) vs weekend (10mg/kg over 2 days) TX for 12 months
- RESULTS: Equally effective for Quantitative muscle testing and MMT (arm and leg) and timed functional testing over 12 months
  - FVC improved 2.8% weekend, 0.6% in Daily
  - Behavior IMPROVED equally in both groups
  - DEXA -lumbar bone density improved in weekend treated cohort, decreased in daily

2011 Escolar, Hache, Clemens, Cnaan, McDonald, Viswanathan, Kornberg, Bertorini, Nevo, Lotze, Pestronk, Ryan, Monasterio, Day, Zimmerman, Arrieta, Henricson, Mayhew, Florence, Hu, Connolly, Neurology 2011

12 sites

CDC: STRONG STATEMENT

- 2010: GLUCOCORTICOIDS- only medication available that
  - slows the decline in muscle strength and function
  - reduces risk of scoliosis
  - stabilizes pulmonary function
  - Improves Cardiac function
- 2013-Prolongs life "All-cause Mortality and Cardiovascular outcomes with prophylactic steroid therapy in DMD" Schram et al, Am J of Am Coll Cardiol, 2013

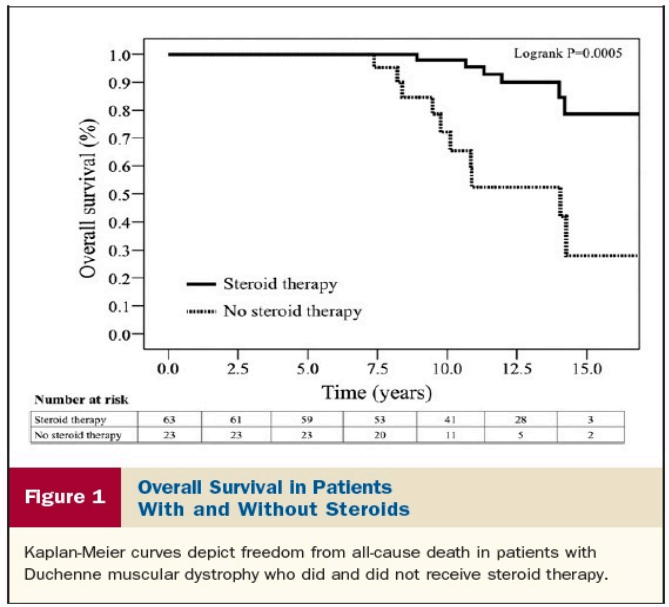
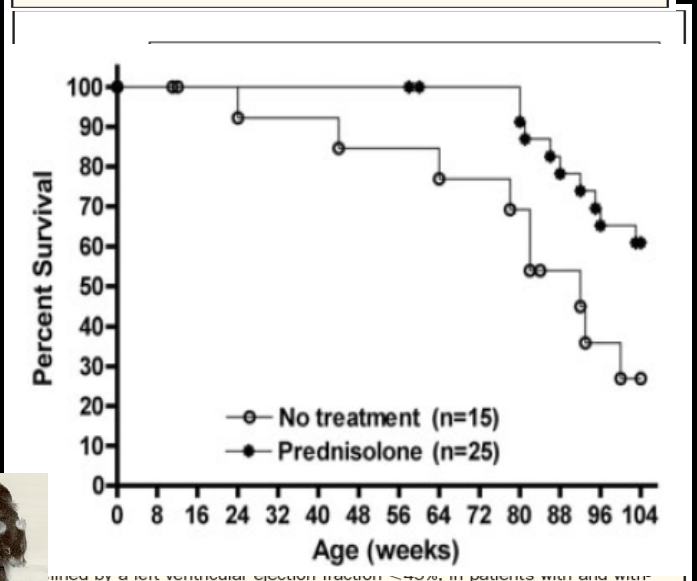
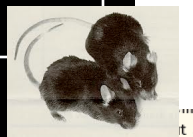


Figure 1 **Overall Survival in Patients With and Without Steroids**

Kaplan-Meier curves depict freedom from all-cause death in patients with Duchenne muscular dystrophy who did and did not receive steroid therapy.





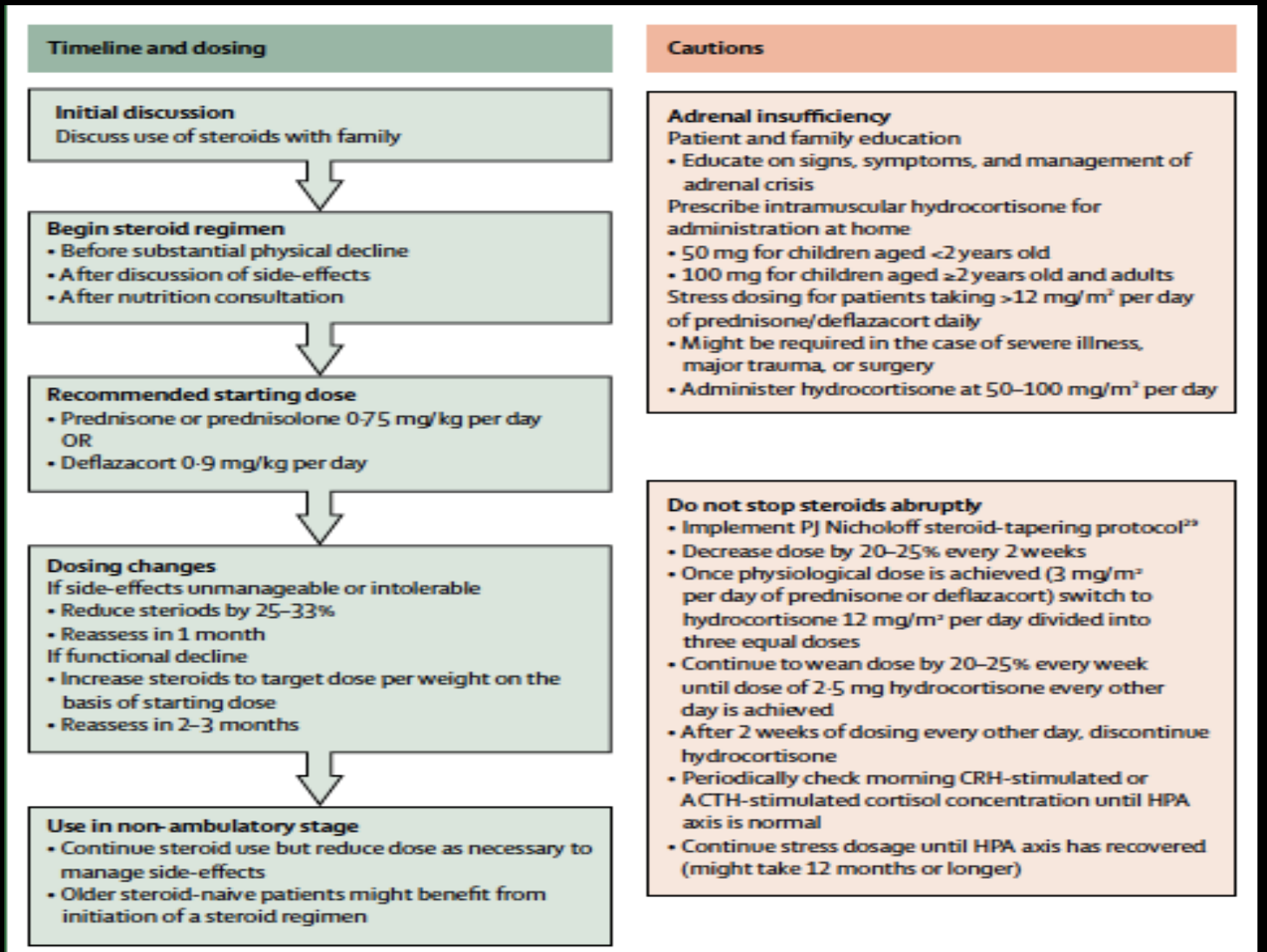
CDC (2010) Corticosteroid Recommendations

- Prednisone 0.75 mg/kg/day
- Deflazacort 0.9 mg/kg/day)
- Alternatives
  - 1) weekend 10mg/kg/week
  - 2) 0.75 mg=1.2 mg/kg every other day
  - 3) 0.75mg/kg/day first 10 days of month
- Washington University standard of care is twice weekly steroids

Duchenne Care Considerations(part 1) 2018

DJ Birnkrant, K Bushby, CM Bann, SD Apkon, A Blackwell, D Brumbaugh, LE Case, PR Clemens, S Hadjiyannakis, S Pandya, NStreet, J Tomezsko, KR Wagner, LM Ward, DR Weber

NB:
Twice weekly
And 10 days on/off not in chart



Timeline and dosing

Initial discussion
Discuss use of steroids with family

Begin steroid regimen
- Before substantial physical decline
- After discussion of side-effects
- After nutrition consultation

Recommended starting dose
- Prednisone or prednisolone 0·75 mg/kg per day
  OR
- Deflazacort 0·9 mg/kg per day

Dosing changes
If side-effects unmanageable or intolerable
- Reduce steriods by 25–33%
- Reassess in 1 month

If functional decline
- Increase steroids to target dose per weight on the basis of starting dose
- Reassess in 2–3 months

Use in non-ambulatory stage
- Continue steroid use but reduce dose as necessary to manage side-effects
- Older steroid-naive patients might benefit from initiation of a steroid regimen

Cautions

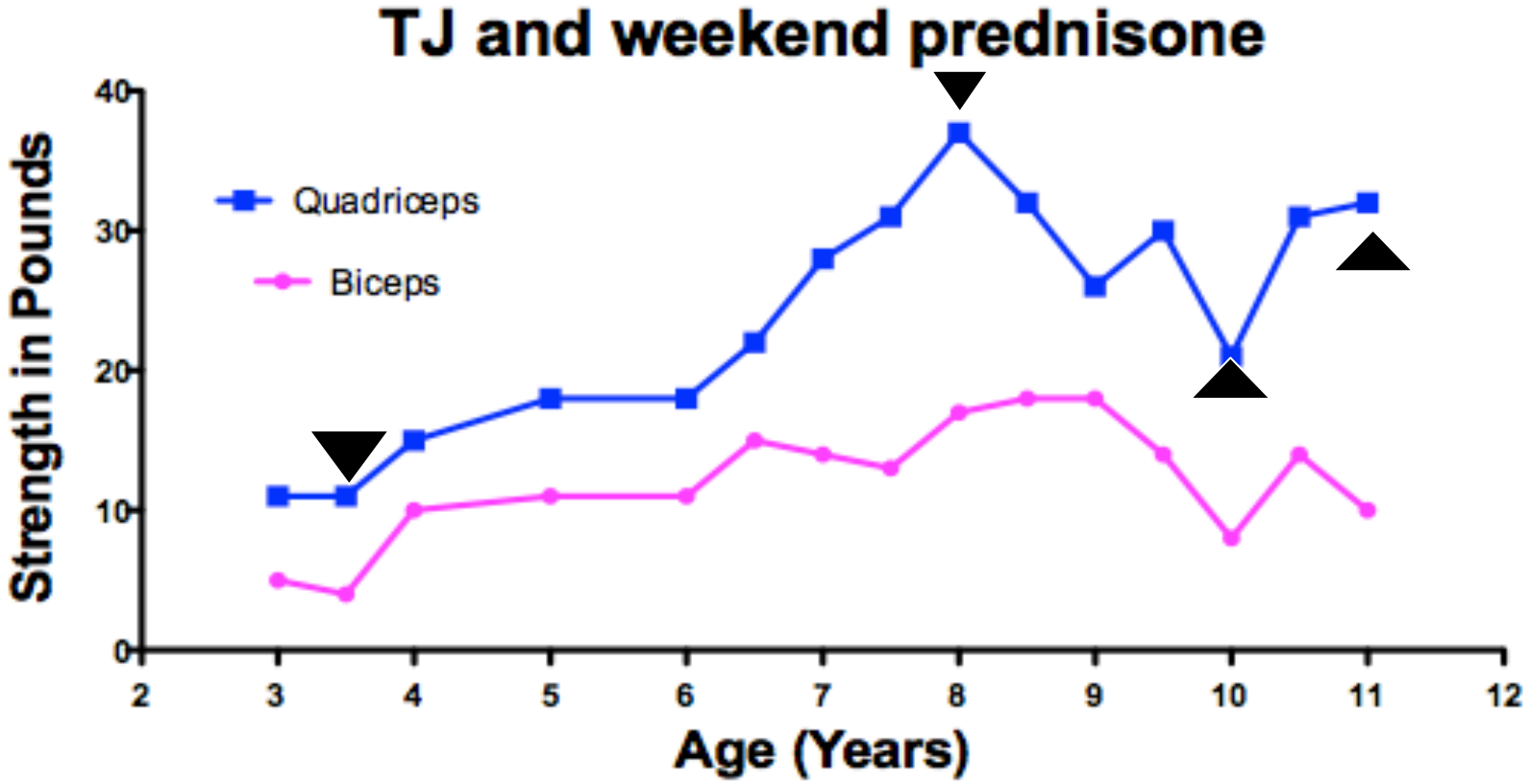
Adrenal insufficiency
Patient and family education
- Educate on signs, symptoms, and management of adrenal crisis

Prescribe intramuscular hydrocortisone for administration at home
- 50 mg for children aged <2 years old
- 100 mg for children aged ≥2 years old and adults

Stress dosing for patients taking >12 mg/m² per day of prednisone/deflazacort daily
- Might be required in the case of severe illness, major trauma, or surgery
- Administer hydrocortisone at 50–100 mg/m² per day

Do not stop steroids abruptly
- Implement PJ Nicholoff steroid-tapering protocol[29]
- Decrease dose by 20–25% every 2 weeks
- Once physiological dose is achieved (3 mg/m² per day of prednisone or deflazacort) switch to hydrocortisone 12 mg/m² per day divided into three equal doses
- Continue to wean dose by 20–25% every week until dose of 2·5 mg hydrocortisone every other day is achieved
- After 2 weeks of dosing every other day, discontinue hydrocortisone
- Periodically check morning CRH-stimulated or ACTH-stimulated cortisol concentration until HPA axis is normal
- Continue stress dosage until HPA axis has recovered (might take 12 months or longer)

Clinical course: Twice weekly Steroids



2003 2012

Steroids are not a cure

- 2010? Who is treating "Everyone?"
- Who is staying on treatment?
- How about after ambulation is lost?

Non-Ambulatory boys/men

N=91 (Collaborating sites: Washington University, Nationwide Children's, UCDavis, Minnesota, Boston)

47 on No Corticosteroids
25 on Daily Corticosteroids
19 on twice Weekly corticosteroids.

Reliable outcomes (ICC >.95) included Vital Capacity, Brooke Scale, Grip strength and Pinch and Key strength.

Corticosteroids benefit non-ambulatory boys and Men

Cortico-steroid Use	FVC % Predicted	Age (Yrs)	Brooke Scale	EK Scale	Grip, Right (Newt)	Grip Left (Newt)	Key Right (Newt)	Key Left (Newt)
Daily n = 25	51 ± 25	16.5± 4.5	**3.2 ± 1.4***	13.1 ± 4.2	**38 ± 23***	34 ± 27	**16 ± 11***	**16 ± 12***
2x week n= 19	**57 ± 20***	15.2 ±3.4	**3.1 ± 1.0***	13.1 ± 3.8	31 ± 18	28 ± 18	13 ± 7	12 ± 7
None n= 47	40± 19	17.5 ±4.7	4.4 ± 1.1	15.7 ± 5.8	19 ± 17	19 ± 17	8 ± 7	7 ± 6

Brooke Scale FVC and hand function better on Corticosteroids: 2014, Connolly et al Muscle and Nerve

Deflazacort

Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy

OPEN

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ABSTRACT

Objective: To assess safety and efficacy of deflazacort (DFZ) and prednisone (PRED) vs placebo in Duchenne muscular dystrophy (DMD).

Methods: This phase III, double-blind, randomized, placebo-controlled, multicenter study evaluated muscle strength among 196 boys aged 5–15 years with DMD during a 52-week period. In phase 1, participants were randomly assigned to receive treatment with DFZ 0.9 mg/kg/d, DFZ 1.2 mg/kg/d, PRED 0.75 mg/kg/d, or placebo for 12 weeks. In phase 2, placebo participants were randomly assigned to 1 of the 3 active treatment groups. Participants originally assigned to an active treatment continued that treatment for an additional 40 weeks. The primary efficacy endpoint was average change in muscle strength from baseline to week 12 compared with placebo. The study was completed in 1995.

Results: All treatment groups (DFZ 0.9 mg/kg/d, DFZ 1.2 mg/kg/d, and PRED 0.75 mg/kg/d) demonstrated significant improvement in muscle strength compared with placebo at 12 weeks. Participants taking PRED had significantly more weight gain than placebo or both doses of DFZ at 12 weeks; at 52 weeks, participants taking PRED had significantly more weight gain than both DFZ doses. The most frequent adverse events in all 3 active treatment arms were Cushingoid appearance, erythema, hirsutism, increased weight, headache, and nasopharyngitis.

Conclusions: After 12 weeks of treatment, PRED and both doses of DFZ improved muscle strength compared with placebo. Deflazacort was associated with less weight gain than PRED.

Classification of evidence: This study provides Class I evidence that for boys with DMD, daily use of either DFZ and PRED is effective in preserving muscle strength over a 12-week period.

Neurology® 2016;87:2123–2131

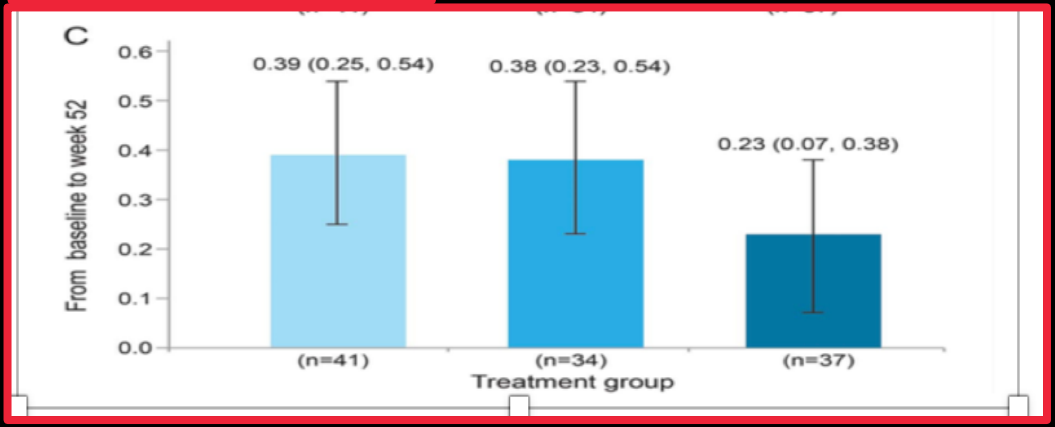
Deflazacort

Table 1 Demographic and baseline characteristics

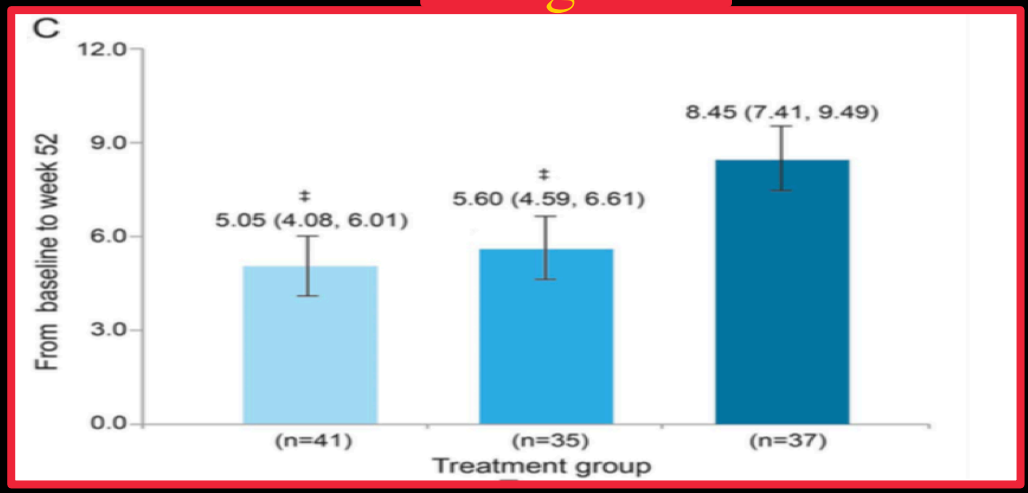
Variable	Deflazacort 0.9 mg/kg/d (n = 51)	Deflazacort 1.2 mg/kg/d (n = 49)	Prednisone 0.75 mg/kg/d (n = 46)	Placebo (n = 50)	Total (n = 196)
Age, y					
Mean (SD)	8.8 (2.5)	8.8 (3.0)	8.8 (2.9)	8.5 (3.1)	8.8 (2.9)
Median	9	8	8	7	8
Min, max	5, 15	5, 15	5, 15	5, 15	5, 15
Male, n (%)	51 (100)	49 (100)	46 (100)	50 (100)	196 (100)
Race, n (%)					
White	46 (90.2)	45 (91.8)	45 (97.8)	49 (98)	185 (94.4)
Asian	0 (0)	1 (2)	0 (0)	0 (0)	1 (0.5)
Other	5 (9.8)	3 (6.1)	1 (2.2)	1 (2.0)	10 (5.1)
Height, cm					
Mean (SD)	131 (17)	130 (20)	131 (18)	130 (18)	131 (18)
Median	128.5	127	127.9	123.1	127.7
Min, max	101.6, 180.0	97.0, 169.6	106.7, 170.0	101.3, 174.0	97.0, 180.0
Weight, kg					
Mean (SD)	31 (13)	29 (11)	32 (15)	31 (15)	30 (14)
Median	26.4	25.5	25.4	23.2	24.7
Min, max	17.1, 73	16.3, 69.5	15.5, 84	14.8, 95	14.8, 95
Body mass index, kg/m^2					
Mean (SD)	17.1 (3.9)	16.7 (3.0)	17.7 (4.2)	17.2 (3.6)	17.2 (3.7)
Median	16.2	16.7	16.2	15.9	16.2
Min, max	9.8, 28.9	9.6, 25.5	12.1, 31.2	12.7, 31.4	9.6, 31.4

Deflazacort (effective and less weight gain than daily corticosteroid treatment)

STRENGTH



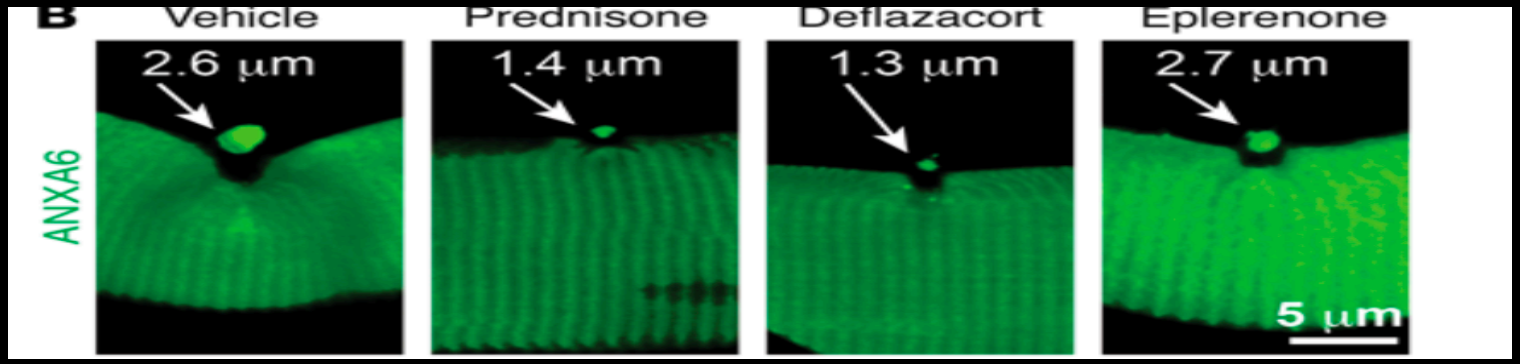
Weight



FDA Approval Feb 2017

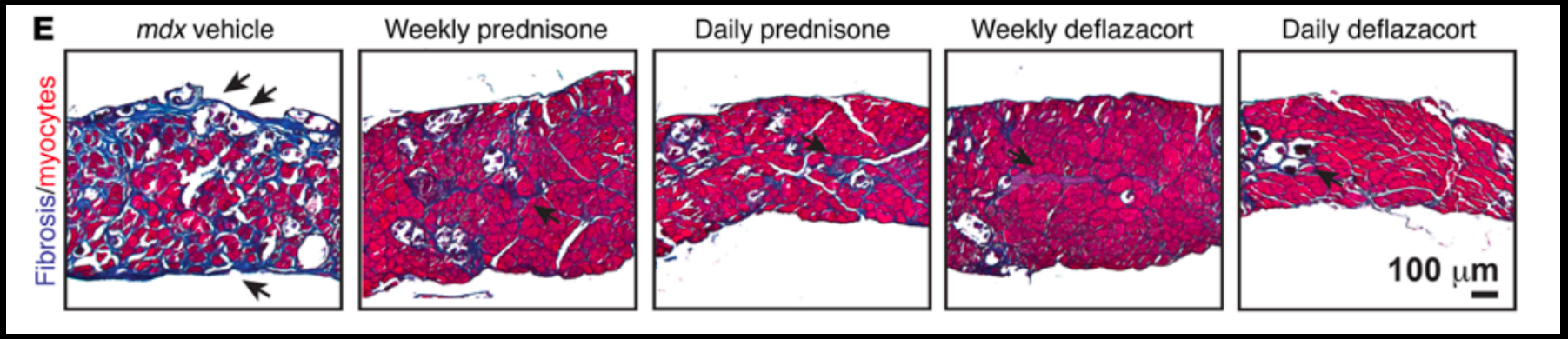
Why do corticosteroids work?

1) Immune suppression? Not via B or T cells (mdx RAG2 mice still develop weakness AND still respond to twice weekly steroids) (Golumbek PT, Keeling RM, Connolly AM. Strength and corticosteroid responsiveness of mdx mice is unchanged by RAG2 gene knockout. Neuromuscul Disord. 2007
2) "Intermittent Glucocorticoid steroid dosing enhances repair without eliciting muscle atrophy" Quattrocelli, Barfield, Warner, Vo, Hadhazy, Early, Domonbreun and McNally JCI 2017
   1) Pulse Steroids (prednisone or deflazacort) result in SMALLER injury after fiber damage from lazer

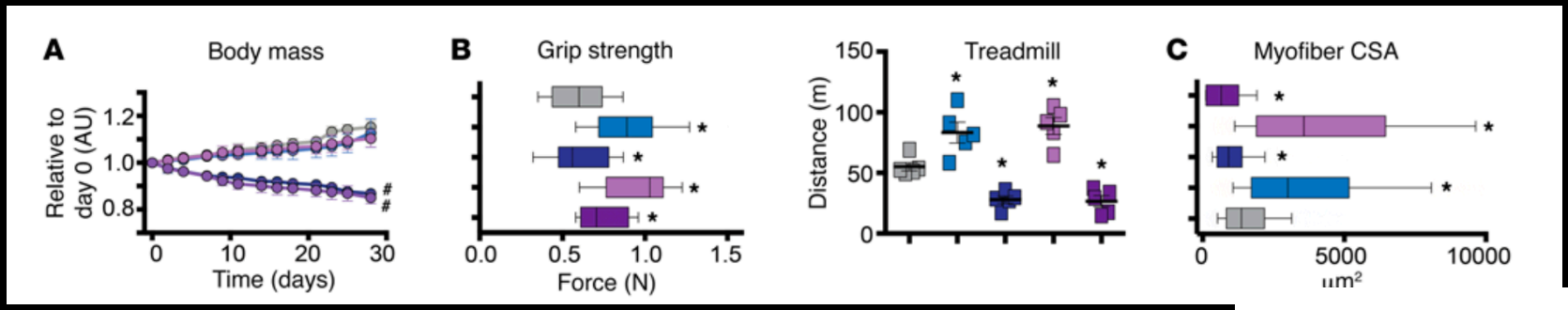


Why do corticosteroids work?

- Repair is improved by daily or weekly corticosteroids

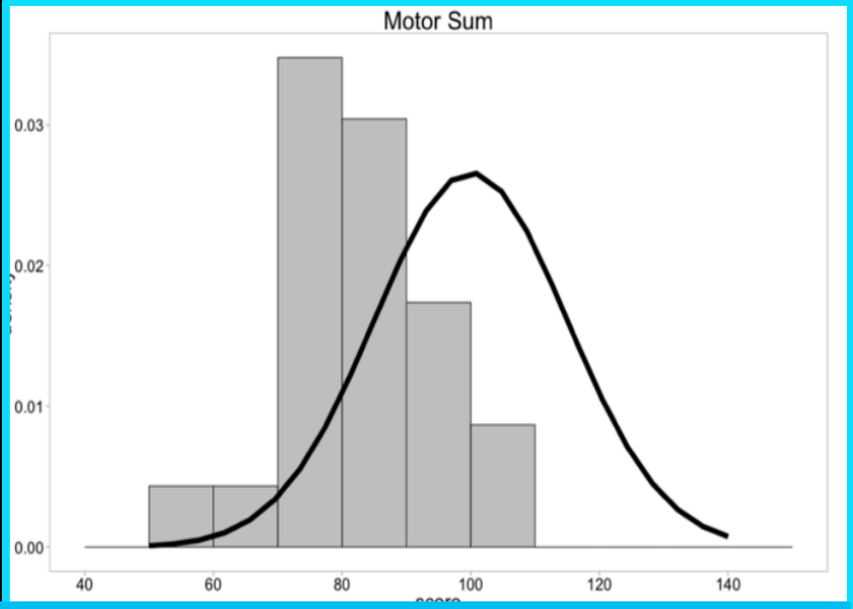


- Atrophy develops only in mdx treated daily

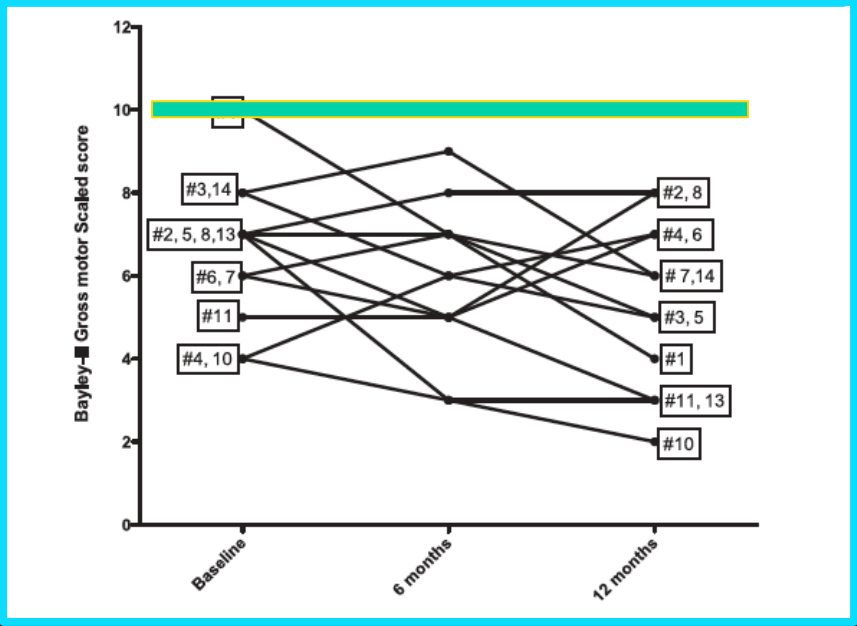


- Quattrocelli, Barfield, Warner, Vo, Hadhazy, Early, Domonbreun and McNally JCI 2017

Infants and young boys with DMD have Gross motor function is measurable and abnormal compared to peers.($p<.0001$)



Infants and young boys with DMD show decline in motor function (Bayley-3) on average in the first years of life.



2014: Pediatric Neurology 2014 Connolly, Florence Cradock et al

Infant outcomes using Bayley-III N=24 (Collaborating sites: Washington University, Nationwide Children's, UCDavis, Minnesota, Boston, Newcastle)

2013: Neuromuscular Disorders: Connolly, Florence, Cradock, et al
2013: Neuromuscular Disorder : Pane et al

Twice weekly corticosteroids and heart function

Objective: Look at LV function before and after 3 months of high dose twice weekly corticosteroids

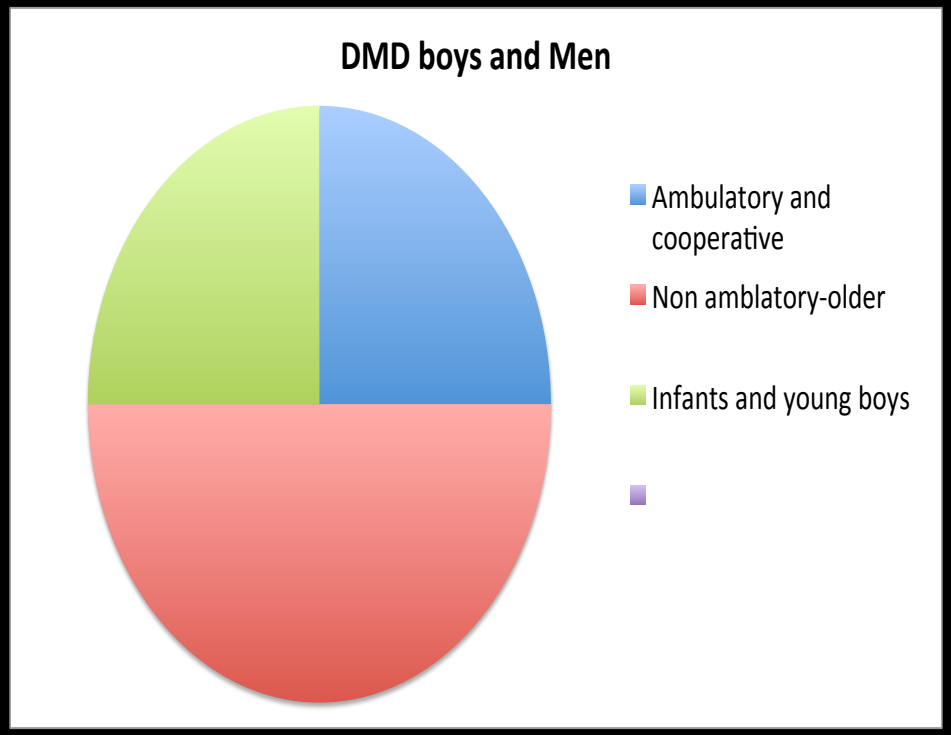
25 with MD, 17 with DMD, 3 with BMD

LV function improved in three month prospective study (10mg/kg over two days) p=0.009 for FS%

	Before Steroids, Mean (SD)	After Steroids, Mean (SD)	*P*
CK, U/L	13,589.6 (14,099.7)	7631 (5587.6)	*0.047**
LVEDD, mm	35.52 (6.8)	33 (6.2)	*0.001†*
LVESd, mm	23.12 (6.13)	23.4 (5)	*0.722*
FS%	32 (8.6)	36.8 (6.8)	0.009†

G Hussein, L Mansour, HA Ghafar, FA Mostafa, L Fawaz 2014J Investig Med 2014;62: 875Y879)

Nearly all clinical trials limited to Ambulatory and "cooperative"

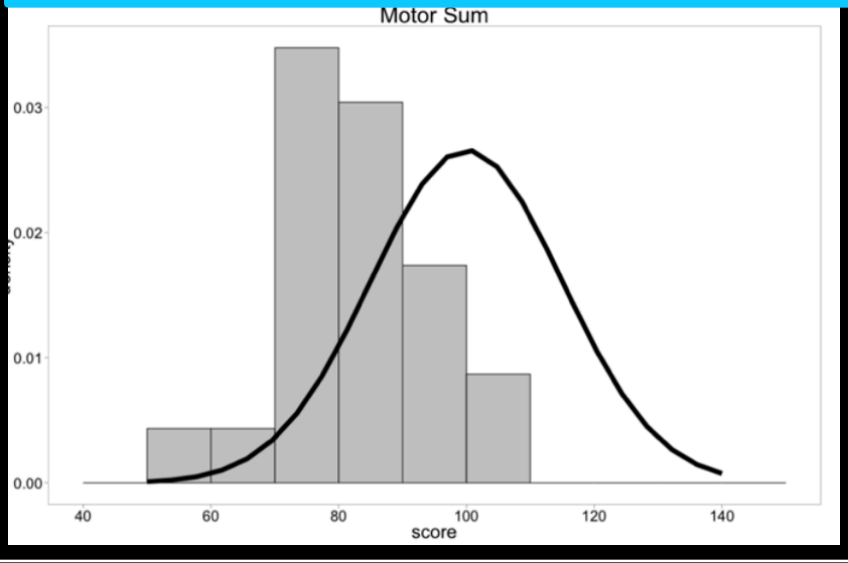


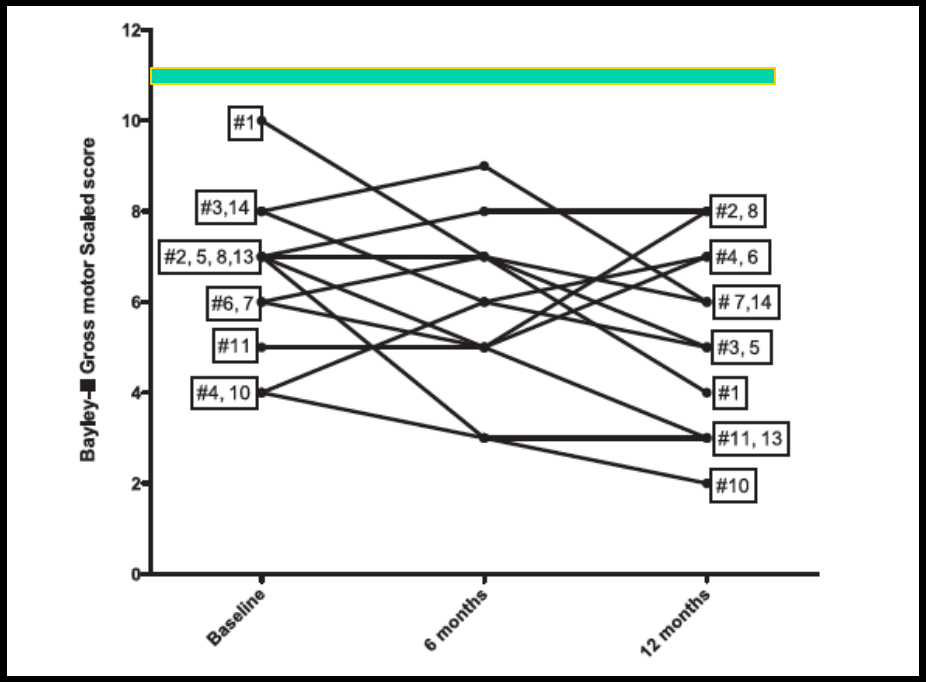
Two problems

1) Some trials (eg rare exons won't be possible using only the 25%
2) Some therapies may work better earlier…or later

MDA-DMD Center grant-develop outcomes

Infant outcomes using Bayley-3 N=24(Collaborating sites: Washington University, Nationwide Children's, UCDavis, Minnesota, Boston, Newcastle)





Infants with DMD have Gross motor function is abnormal compared to peers.
2013: Neuromuscular Disorders: Connolly, Florence, Cradock, et al
2013: Neuromuscular Disorder : Pane et al

In young boys with DMD Bayley-3 Gross motor function declines on average in the first years of life: 2014: Pediatric Neurology 2014 Connolly, Florence Cradock et al

Clinical Trial complete: Does twice weekly corticosteroids improve Bayley 3 Gross Motor function in children less than 30 months? Short answer yes, paper in Review in Neurology

Dream slide:
DMD and BMD Diagnosis At Birth
(as part of Newborn screening)

Mutation Specific Therapy

Mutation Non- Specific Therapy

Early intervention for Cognitive Impairment

Increase walking to age 30-60; lifespan normal

Many thanks to

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Part of Bayley exam of 40 month old with DMD: Cognitive and Social 25%ile; Motor 5th %ile