Corticosteroids and an Overview of Neuromuscular Care

Edward C. Smith, MD
Duke Children’s Hospital
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
Why Corticosteroids?

• 1989: Clinical Investigation in DMD (CIDD) group (Mendell JR, et al): RCT showing short-term benefits on muscle strength, timed function tests and FVC

Mendell JR, et al., *NEJM* 1989

**Figure 1.** Change (Mean ± SEM) in the Score for Average Muscle Strength in the Placebo and Prednisolone Groups after the Initiation of Their Regimens.

The solid line (“natural history”) represents the values for change observed in 177 patients with Duchenne’s muscular dystrophy who received no treatment.⁸,¹²
Why Corticosteroids?

- Decreased incidence/severity of scoliosis:

Fig. 1
Kaplan-Meier survival curve for the proportion of boys in whom a curve of ≥20 did not develop at each year following the enrollment in the trial. There was a significant difference ($p = 5.8 \cdot 10^{-27}$) in the chance of a curve of ≥20 developing between the treatment and non-treatment groups. Ninety-five percent confidence intervals are given for all of the points following enrollment in this study.

Alman B, et al., JBJS 2013
Why Corticosteroids?

Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators*

- CINRG DMD Natural History Study
  - N=440 with 10-year follow-up
  - GC-tx increased median age at loss of mobility milestones by **2.1-4.4 y** and upper limb milestones by **2.8-8.0 y**
  - GC-tx associated with **improved overall survival**:  
    - Of 39 deaths, 9% (> 1 y on GC – 28/311) vs. 19% (< 1 mo GC use – 11/58) (p=0.0501)
  - Age at loss of ambulation **10 y** (<1 mo GC) vs **13.4 y** (>1 y GC)
  - Milestone transitions tended to be more delayed in DFZ- vs. Pred-treated patients

McDonald C, et al., *Lancet* 2017
**E Age at loss of ambulation**

<table>
<thead>
<tr>
<th>Patients reaching milestone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>75</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

**Number at risk**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>&lt;1 month glucocorticoid use</th>
<th>≥1 year glucocorticoid use</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>73</td>
<td>330</td>
</tr>
<tr>
<td>73</td>
<td>26</td>
<td>329</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>223</td>
</tr>
<tr>
<td>0</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median age at event, years (SE; 95% CI)**

- <1 month glucocorticoid use: 10.00 (0.33; 9.30 to 10.80)
- ≥1 year glucocorticoid use: 13.40 (0.29; 12.50 to 14.00)

p < 0.0001

McDonald C, et al., *Lancet* 2017
Corticosteroids

• DMD Care Considerations (Lancet 2010) – update is on the way

• When to start?
  – Individual decision (consider functional state, age)
  – Not recommended for boys still gaining motor skills (generally under age 4 y in DMD)
  – Start discussion before plateau phase
  – Make sure immunizations are complete
**TIMELINE/DOSING**

**Initial Discussion**
Discuss steroids with family

**Begin Steroid Regimen**
- Before significant physical decline
- After discussion of side effects
- After nutrition consult

**Recommended Starting Dose**
Prednisone/prednisolone 0.75 mg/kg/day

**Dosing Changes**
- If side effects unmanageable/intolerable
  - Reduce steroids by 25–33%
  - Reassess in 1 month
- If functional decline
  - Increase steroids to target dose per weight based on 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-naïve patients may benefit from initiating a steroid regimen

**CAUTIONS**

**Adrenal Insufficiency**
- **Patient/family education**
  - Educate on signs, symptoms, and management of adrenal crisis
- **Prescribe intramuscular hydrocortisone for administration at home**
  - 50 mg for children < 2 yrs old
  - 100 mg for children/adults ≥ 2 yrs old
- **Stress dosing for patients taking > 12 mg/m²/day of prednisone/deflazacort daily**
  - May be required when severe illness, major trauma, or surgery
  - Administer hydrocortisone at 50–100 mg/m²/day

**DO NOT STOP STEROIDS ABRUPTLY**
- Implement PJ Nicholoff steroid-tapering protocol
- Decrease dose by 20–25% every 2 weeks
- Once physiologic dose is achieved (3 mg/m²/day of prednisone/deflazacort) switch to hydrocortisone 12 mg/m²/day divided into 3 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 every other dosing, discontinue hydrocortisone
- Periodically check AM- or CRH-/ACTH-stimulated cortisol level until HPA axis is determined normal
- Continue stress dosage until HPA axis has recovered. May take 12 months or longer.
Corticosteroids

- If SEs from daily dosing intolerable, consider dose reduction or alternative dosing strategies (see Table 3):

<table>
<thead>
<tr>
<th>Prednisone dose*</th>
<th>Deflazacort dose*</th>
<th>Comments</th>
<th>In case of side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate day</td>
<td>0-75-1.25 mg/kg</td>
<td>2 mg/kg every other day</td>
<td>Less effective but consider when a daily schedule has side-effects that are not effectively managed or tolerated</td>
</tr>
<tr>
<td>High-dose weekend</td>
<td>5 mg/kg given each Friday and Saturday</td>
<td>Not yet tested</td>
<td>Less data on effectiveness as compared to a daily schedule. Consider as an alternative to daily treatment, especially if weight gain and behavioural issues are problematic</td>
</tr>
<tr>
<td>Intermittent</td>
<td>0.75 mg/kg for 10 days alternating with 10-20 days off medication</td>
<td>0.6 mg/kg on days 1–20 and none for the remainder of the month</td>
<td>Less effective but has fewer side-effects. Consider as the least effective but possibly best tolerated regimen before abandoning steroid treatment altogether</td>
</tr>
</tbody>
</table>

*No set dose ranges have been clearly accepted as optimum.
Corticosteroids

• What to monitor?
  – See Table 2 (next slide) in Care Guidelines for specific recommendations re: monitoring and intervention
  – Appreciate the impact on self-image/self-esteem: obesity, hirsutism, growth retardation, delayed puberty
    • for some boys these are just as important as the disease itself
  – Bone health, testosterone and growth hormone – to be covered by Dr. DiVall a bit later today
Corticosteroids

<table>
<thead>
<tr>
<th>Constitutional and cosmetic</th>
<th>*Particular vigilance needed if patient, parents, or siblings are obese Dietary advice to be reinforced before starting steroids; warn about increased appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushingoid features, obesity</td>
<td>(o) Implement proactive dietary management for the entire family, not just the patient Consider change from prednisone to deflazacort Select an alternative regimen</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>(o) Does not usually occur to an extent that warrants a change in medication Use ancillary treatment measures (topical prescription) and do not rush to change the GC regimen unless the boy is emotionally distressed</td>
</tr>
<tr>
<td>Acne, tinea, warts</td>
<td>(o) More notable in teenagers Use topical treatments</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>(o) Consider endocrine evaluation if growth plateaus</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>(o) Monitor height at least every 6 months as part of general care (stature tends to be small in DMD even without steroid treatment) Consider endocrine assessment if notably delayed or patient is upset by the delay</td>
</tr>
<tr>
<td>Adverse behavioural changes</td>
<td>(o) Identify any baseline mood, temperament, ADHD issues, and advise parents that these often transiently worsen in the initial 6 weeks on GC therapy Decide whether baseline issues should be treated before starting GC therapy (eg, ADHD counselling or prescription) Consider changing timing of GC medication to later in the day Consider behavioral health referral</td>
</tr>
<tr>
<td>Immune/adrenal suppression</td>
<td>(o) Advise parents of risk of serious infection and need to promptly address minor infection Advise parents to inform all medical personnel that their child is on steroids and carry steroid alert card Ensure that the GC is not stopped abruptly Obtain varicella immunisation before starting GC therapy; confirm with protective serum titre Engage in tuberculosis surveillance Obtain infectious diseases consultation if serious infection occurs Substitute prednisone equivalent if deflazacort is temporarily unavailable Implement Intravenous stress-dose hydrocortisone or methylprednisolone coverage for surgery or major illness (no accepted treatment strategy; anaesthesia or endocrine consultation recommended) Give intravenous coverage if nothing by mouth</td>
</tr>
<tr>
<td>Hypertension</td>
<td>(o) Monitor blood pressure as percentiles for height and sex at each clinic visit If blood pressure &gt;95%, reduce salt intake; weight reduction If ineffective, refer for possible ACE inhibitor or (\beta) blocker medication</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>(o) Urine dipstick for glucose at clinic visits If urine is glucose-positive, then try fasting or post-prandial blood glucose, and if abnormal, then seek an endocrine consultation</td>
</tr>
<tr>
<td>GERD</td>
<td>(o) Enquire about GERD symptoms (heartburn) Avoid NSAIDs</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>(o) Advise parents of risk and to report symptoms Avoid NSAIDs</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>(o) History of gastritis, GERD, abdominal pain, or faecal blood</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>(o) Test stool for blood if anaemic or suggestive history</td>
</tr>
<tr>
<td>Cataracts</td>
<td>(o) Annual ophthalmological examination</td>
</tr>
<tr>
<td>Bone demineralisation and increased fracture risk</td>
<td>(o) Take careful fracture history For 25-hydroxy vitamin D concentration 20–31 nmol/L, give 1000 IU orally twice daily, for &lt;20 nmol/L, give 2000 IU orally twice daily</td>
</tr>
<tr>
<td>Bone demineralisation and increased fracture risk</td>
<td>(o) Annual monitoring of 25-hydroxy vitamin D blood concentration (ideally late winter in seasonal climates) and supplement with vitamin D3 if level &lt;32 nmol/L Consider bisphosphonates, such as pamidronate</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>(o) Enquire about abnormal coloration of urine after exercise, urinary testing A dusky appearance of excessive ecchymosis (eg, descending stairs, squatting down, trampering) and restless exercise Commence renal investigations if persistent</td>
</tr>
</tbody>
</table>

Common chronic side-effects of high-dose GC administration in growing children are listed for the ambulatory and non-ambulatory patient who has DMD, assuming typical initiation of prednisone or deflazacort at age 6 years (+2) and continued use on a daily schedule. \(\text{w}^{15,16}\) Reduction in dose is necessary if side-effects are unmanageable or intolerable. If this is unsuccessful, then further reduction or change to another dosing regimen is necessary before abandoning treatment altogether (figure 5). Close monitoring for side-effects is important, especially within the initial 6 months of treatment. ACI—an angiotensin converting enzyme, ADHD—attention-deficit hyperactivity disorder, DEXA—dual-energy a\-ray absorptiometry, DMD—Duchenne muscular dystrophy, GC—glucocorticoid, GERD—gastroesophageal reflux disease. NSAID—non-steroidal anti-inflammatory drug. \*See part 2 of this Review (figure 1).
Corticosteroids

Starting GCs

- **Prednisone**
  - 0.75 mg/kg/day
  - First line unless pre-existing weight and/or behavioural issues favour deflazacort

- **Deflazacort**
  - 0.9 mg/kg/day
  - Consider as first line when pre-existing weight and/or behavioural issues

**Age <2 years**
- Improving (typical): GC initiation not recommended
- Plateau (uncommon): monitor closely
- Decline (atypical): consider alternative diagnoses/concomitant pathology

**Age 2-5 years**
- Improving: GC initiation not recommended
- Plateau: GC initiation recommended
- Decline: GC initiation highly recommended

**Age ≥6 years**
- Improving (uncommon): consider BMD
- Plateau: GC initiation highly recommended
- Decline: GC initiation highly recommended
- 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

Monitoring side-effects and factors to consider when using GCs

- If any side-effects are manageable and tolerable
  - Incremental increase in dose for growth to maximum weight of 40 kg (prednisone 30 mg/day or deflazacort 36 mg/day)
  - If in functional decline and on subtarget dose, increase to target dose
  - Continue even when non-ambulatory for retarding of scoliosis, decline in pulmonary function tests, and possibly heart failure

- If any side-effects are unmanageable and intolerable, then a change in GC regimen is necessary
  - Reduce daily dosage by 25-33% and reassess in 1 month
  - If side-effects are still unmanageable and intolerable
    - Consider lowering additional 25% on daily schedule; minimum effective daily dose of prednisone is approximately 0.3 mg/kg/day
    - If weight gain/behaviour are main issues, consider change to deflazacort or high-dose weekend
    - If patient/parents are about to abandon treatment entirely, consider 10/10 or 10/20 intermittent schedule

*Figure 4: Schema for initiation and management of GC medication in Duchenne muscular dystrophy*. See table 2 for more on monitoring side-effects. BMD = Becker muscular dystrophy. GC = glucocorticoid.
Steroids 101

• Most important aspect of starting GC-therapy – caregiver/patient MUST understand the risks, esp. adrenal insufficiency/adrenal crisis

• “Steroid factory” explanation

• Also, explain that corticosteroids ≠
Corticosteroids

• Safety – PJ Nicholoff Steroid Protocol (Kathi to cover tomorrow)
  – Missed doses, stress dosing
  – Signs of adrenal insuff/crisis (may be really non-specific)
    • Fatigue, nausea, headache, light-headedness….
  – Don’t assume the ED/surgeon knows

• EDUCATE your families/patients – and make sure they are comfortable speaking up and educating people in white coats (this is a big issue)

• Ask caregiver/patient to teach back – go through a few scenarios in clinic, it doesn’t take long
Neuromuscular Care

- Neuromuscular and skeletal management

**Assessments**
- Clinical evaluation
- Strength
- Function
- ROM

**Considerations**
- Age of patient
- Stage of disease
- Risk factors for side-effects
- Available GCs
- Choice of regimen
- Side-effect monitoring and prophylaxis
- Dose alteration

**Tools**
- Creatine kinase
- Genetic testing
- Muscle biopsy

**Interventions**
- Genetic counselling
- Family support

**Diagnoses**

**Rehabilitation management**

**Corticosteroid management**

**Orthopaedic management**

**Psychosocial management**

**Family**

Patient with DMD

**Tools**
- Spirometry
- Pulse oximetry
- Capnography
- PCF, MIP/MEP, ABG

**Interventions**
- Volume recruitment
- Ventilators/interfaces
- Tracheostomy tubes
- Mechanical insufflator/exsufflator

**Tools**
- ECG
- Echo
- Holter

**Interventions**
- ACE inhibitors
- β blockers
- Other heart failure medication

**Assessments**
- ROM
- Strength
- Posture
- Function
- Orthoses
- Alignment
- Gait

**Interventions**
- Stretching
- Positioning
- Splinting
- Submaximum exercise/activity
- Seating
- Standing devices
- Adaptive equipment
- Assistive technology
- Strollers/scooters
- Manual/motorised wheelchairs

**Diagnostics**

**Pulmonary management**

**Cardiac management**

**Tools**
- Assessment of ROM
- Spinal assessment
- Spinal radiograph
- Bone age (left wrist and hand radiograph)
- Bone densitometry

**Interventions**
- Tendon surgery
- Posterior spinal fusion

**Tools**
- Coping
- Neurocognitive
- Speech and language
- Autism
- Social work

**Interventions**
- Psychotherapy
- Pharmacological
- Social
- Educational
- Supportive care

**Management of other complications**

**Tools**
- Upper and lower GI investigations
- Anthropometry

**Interventions**
- Diet control and supplementation
- Gastrostomy
- Pharmaco logical management of gastric reflux and constipation
Neuromuscular Care

• **Corticosteroid Management** (Done)

• **Rehabilitation Management** (tomorrow – Heather and Claudia)
  – ROM/strength/function/posture/gait assessments: done in each clinic by PT (beware of redundancy)
  – Orthotics, DME needs: PT/OT, DME vendor

• **Diagnostics**…

• **Orthopedic Management**…
# Neuromuscular Care

## Stage 1: Presymptomatic
- Can be diagnosed at this stage if creatine kinase found to be raised or if positive family history
- Might show developmental delay but no gait disturbance

### Diagnostics
- Diagnostic examination and genetic counselling

### Neuromuscular management
- Anticipatory planning for future developments
- Ensure immunisation schedule is complete

### Orthopaedic management
- Orthopaedic surgery rarely necessary

### Rehabilitation management
- Education and support
  - Preventive measures to maintain muscle extensibility/ minimise contracture
  - Encouragement of appropriate exercise/activity
  - Support for function and participation
  - Provision of adaptive devices, as appropriate

## Stage 2: Early ambulatory
- Gowers’ sign
- Waddling gait
- Might be toe walking
- Can climb stairs

## Stage 3: Late ambulatory
- Increasingly laboured gait
- Losing ability to climb stairs and rise from floor

### Stage 4: Early non-ambulatory
- Might be able to self propel for some time
- Able to maintain posture
- Might develop scoliosis

### Stage 5: Late non-ambulatory
- Upper limb function and postural maintenance is increasingly limited

### Consider surgical options for TA contractures in certain situations

### Monitor for scoliosis: intervention with posterior spinal fusion in defined situations

### Possible intervention for foot position for wheelchair positioning

### Continue previous measures
- Provision of appropriate wheelchair and seating, and aids and adaptations to allow maximum independence in ADL, function, and participation

## Likely to be diagnosed by this stage unless delayed for other reasons (e.g. concomitant pathology)
- Continue assessment to ensure course of disease is as expected in conjunction with interpretation of diagnostic testing
- At least 6-monthly assessment of function, strength, and range of movement to define phase of disease and determine need for intervention with GCs, ongoing management of GC regimen, and side-effect management
Diagnostics

- Suspect DMD (ie, check CPK) in any boy referred to you for “motor delay”, “hypotonia”, “weakness”, “toe walking”, “ADHD”… even you don’t agree with referring MD
- Discuss your concern for DMD and why you want to send genetic testing before sending it
  - Discuss the possible implications of the testing
  - Time follow-up appointment accordingly allowing enough time at the visit for counseling, listening
- Rarely a role for muscle biopsy
  - Negative genetic testing, but still suspect DMD
  - Novel mutation with unknown effect on protein; no other affected family members
- No role for EMG/NCS
- Remind all of your colleagues, esp. in GI, that ALT and AST are liver AND MUSCLE transaminases
- http://www.childmuscleweakness.org
- https://motordelay.aap.org
Neuromuscular Care

Orthopedic Management (later today - Dr. DiVall)

• Contractures and scoliosis
  – LE contractures (IT band, HF, KF, AF); value of surgical contracture release remains uncertain
  – Surgery has to be individualized; make every effort to mobilize ASAP post-operatively (this goes for fractures as well)
  – Spine
    • 90% of patients not on CS will develop progressive scoliosis
    • Scoliosis monitoring:
      – Full-spine xray for ambulatory patients with clinical suspicion
      – Full-spine xray for non-ambulatory patients (get baseline around time of LOA)
      – Repeat q 12 months for Cobb angle < 20º, q6 months for Cobb angle > 20º
      – Reduce frequency after reaching skeletal maturity
    • Repeat for new-onset back pain to look for vertebral fracture
    • PSF:
      – Warranted in non-ambulatory patients with Cobb angle > 20º, NOT taking CS and have not reached skeletal maturity
      – Consider in non-ambulatory patients taking CS if Cobb angle > 40º
Roles and Responsibilities of the Neuromuscular Specialist in the Care of DMD Patients

- Assess and characterize each patient’s unique trajectory of DMD over time using validated assessment tools, aiming to determine a patient’s expected clinical course and to advise on prognosis and potential complications.

- Use assessment information to select the therapeutic interventions that define a customized treatment plan that is designed to meet the particular needs and goals of each patient and family, optimizing outcomes and quality of life as defined by the patient himself.

- Engage the specific clinicians who can enact the designated assessments, interventions, and treatment plan, ideally in the context of a dedicated, multidisciplinary DMD clinic that is led, administered, and coordinated by the NMS. Assist in the care of female carriers, including cardiac evaluation.

- Be the first-line medical advisor to patients and their families as they define and revise their individual care goals over time, helping them personalize their risk/benefit analysis of potentially beneficial therapeutic interventions, including:
  - Technological interventions regarding pulmonary and cardiac management.
  - Surgical and nonsurgical interventions, such as spinal fusion, contracture management, and provision of aids and appliances.
  - Pharmacological interventions, such as glucocorticoid therapy, emerging therapies, and patient participation in clinical research trials of investigational drugs.

- Be an advocate for high-quality DMD care at their institutions and in their communities, regarding issues such as transition of care from pediatric to adult clinical providers and provision of hospital care that is designed to address the unique medical, physical, and psychosocial needs of DMD patients.

- Help patients and families navigate end-of-life care in a way that preserves comfort, dignity, and quality of life as defined by each individual patient and his family.
Questions/Comments?

• 10:30-11:00 – BREAK

• 11:00-11:30 – Pulmonary Care (Dr. Taylor)