Muscular Dystrophy and Adrenal Suppression
The PJ Nicholoff Steroid Protocol for Duchenne and Becker

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chronic use of corticosteroids is associated with significant side effects that require monitoring and treatment. In the late 1980's, it was established that corticosteroids could improve and prolong ambulation and slow the rate of decline in heart disease and heart failure, and typically occur in the mid-20s, though survival into the 30s is no longer uncommon.

assisted ventilation and other interventions, the median life expectancy was age 19; however, today most deaths are due to progressive respiratory muscle weakness, which leads to hypoventilation, respiratory insufficiency, and respiratory failure in old without treatment, though ambulation can be extended by one or two years through the use of corticosteroids. There is typically made between 3 and 5 years of age. Progressive muscle weakness leads to the loss of ambulation at 10 to 12 years old without treatment, though ambulation can be extended by one or two years through the use of corticosteroids. There is progressive respiratory muscle weakness, which leads to hypoventilation, respiratory insufficiency, and respiratory failure in adulthood. There is also a progressive cardiomyopathy leading to cardiac insufficiency. Prior to the use of corticosteroids, assisted ventilation and other interventions, the median life expectancy was age 19; however, today most deaths are due to heart disease and heart failure, and typically occur in the mid-20s, though survival into the 30s is no longer uncommon.

In the late 1980's, it was established that corticosteroids could improve and prolong ambulation and slow the rate of decline in both Duchenne and Becker. The use of corticosteroids has also reduced the incidence and severity of scoliosis. However, chronic use of corticosteroids is associated with significant side effects that require monitoring and treatment.

International consensus recommendations on the comprehensive care for people living with Duchenne were published in Lancet

PLOS Currents Muscular Dystrophy
Given the multi-systemic nature of the disease, there should generally be an interdisciplinary team of care providers with whom to consult, including, at minimum, a coordinator, neurologist, doctor of physical medicine and rehabilitation, pulmonologist, cardiologist, social worker, dietician and primary care doctor. However, one issue in the management of Duchenne is that due to increased life expectancy, patients at some point need to transition out of pediatric care and on to adult care teams. Although the transition into adult care should be a process, clinicians in the emergency department should be aware that it is sometimes delayed or incomplete — and may in fact be triggered by the very acute illness or clinical event that brings them to the emergency room (ER).

While any illness or trauma may occur in a person with Duchenne or Becker, certain clinical scenarios are more common. These include exacerbations of the underlying respiratory or cardiac disease; kidney stones; and fractures as a result of low bone mineral density. Patients with Duchenne also seem to be prone to a particularly devastating consequence of fracture, fat embolism syndrome. Each medical crisis needs to be evaluated and responded to in the context of the expected complications of the disease or medications used for disease management — particularly the chronic use of corticosteroids, which can lead to suppression of the hypothalamus-pituitary-adrenal axis (HPA).

One danger is that, as pressing medical emergencies emerge, issues of daily medical care (including medications) may be pushed aside. However, the consequences of suddenly discontinuing or not appropriately dosing corticosteroids, particularly during a crisis can be quite severe, as the patient may have little to no ability to produce cortisol in response to stress. An additional issue for emergency departments is that many patients with Duchenne or Becker use Deflazacort, a corticosteroid that was recently approved in the United States but may be unfamiliar to doctors.

A recent case in point involved Phillip James “PJ” Nicholoff, a vibrant, 31-year-old man living with Duchenne muscular dystrophy. PJ had been treated with daily corticosteroids since the age of 6. He endured several pathologic fractures, likely a result of his steroid treatment and his non-ambulatory status. In November 2013, on a trip to Florida, he fractured his humerus and hip, and was transported by plane to a hospital closer to his home in the north. PJ had orthopedic surgery to manage both of these fractures. Following the surgery, however, he developed respiratory distress, tachycardia, hypotension, and later died. A review of the medical record suggested that he had not received appropriate stress-doses of steroids during his hospitalization. While PJ’s death may have been attributed to many causes, inadequate corticosteroid doses may have been a contributing factor. Consequently, experts in the field held extensive discussions in order to develop a protocol on steroid dosing during an acute illness or other emergency.

The protocol addresses several issues:

- How to define HPA suppression in a patient using corticosteroids
- Appropriate corticosteroid stress doses for minor, moderate, and major stressors
- Recommendations for corticosteroid withdrawal
- How to test the HPA axis for continued suppression
- Symptoms of acute adrenal crisis
- Tests that can help diagnose adrenal crisis
- Corticosteroid conversions/equivalent doses

**The PJ Nicholoff Steroid Protocol**

**1. Background/Assessment**

The normal basal secretion of cortisol from the adrenal gland is approximately 5-7 mg/m²/day in children or 8-10 mg/day for adults. This amount increases during minor illnesses or surgery to approximately 50 mg/day (5x normal physiologic secretion), and typically return to baseline in 24 hours. Severe illness, trauma, or major surgical procedures cause increased cortisol production to about 75-150 mg/day (10x normal physiologic secretion), which return to baseline in about 5 days.

Long-term administration of corticosteroids (primarily prednisone, prednisolone or deflazacort) may lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis, such that the adrenal glands no longer produce endogenous cortisol. Rapid reduction or abrupt withdrawal of corticosteroid therapy can cause secondary adrenal insufficiency and steroid withdrawal or deprivation syndrome, which may progress to adrenal crisis. Adrenal crisis is characterized by hypotension and hypovolemic shock, which may be life threatening. Recovery from suppression of the HPA axis after discontinuing corticosteroids can be prolonged (possibly 6 to 12 months) and may vary based on doses, dosing schedules and duration of corticosteroid therapy. Since there is a great deal of individual variability, it is not possible to predict with confidence which patients will be affected by adrenal suppression. Current practice is to administer supplemental (stress) doses of corticosteroids to patients with possible suppression of the HPA axis in the perioperative period and during acute illness to prevent acute adrenal insufficiency, or adrenal crisis.
2. Defining HPA Suppressed Patients:
Recommendations differ slightly in defining a suppressed patient, but general guidelines are as shown in table 1. These recommendations are primarily based on expert opinion and practice, as little data in this area have been published, but are based on the degree of medical/surgical stress and the likelihood of adrenal suppression. Consultation with an endocrinologist is recommended for questions or concerns.

<table>
<thead>
<tr>
<th>Prednisone dose Equivalents/day - Adults</th>
<th>Prednisone Dose Equivalents/Day - Pediatric</th>
<th>Suppression of HPA axis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mg/day or less</td>
<td>3 mg/m2/day or less</td>
<td>Usually not suppressed.</td>
</tr>
<tr>
<td>5 – 20 mg/day</td>
<td>3-12 mg/m2/day</td>
<td>Possibly suppressed. ACTH stimulation test recommended or give supplemental dose.</td>
</tr>
<tr>
<td>20 mg/day for &gt;10 days or more</td>
<td>12 mg/m2/day of prednisone for &gt; 10 days or more</td>
<td>Suppressed. Give supplemental dose.</td>
</tr>
</tbody>
</table>

Table 1: Defining Adrenal Suppression. Note: doses for prednisone and prednisolone are equivalent; conversion is required for patients taking deflazacort (5 mg prednisone or prednisolone = 6 mg deflazacort)

Patients receiving disease appropriate corticosteroid doses (at least 10 times above the physiologic cortisol dose) generally do not need stress doses if usual daily dose is continued. Patients who are on maintenance physiologic dose of hydrocortisone for primary disease of the HPA axis do require supplemental therapy. Recommendations for supplemental doses are generally divided by the severity of the stress the patient may experience (medical or surgical).

3. Corticosteroid Stress Doses for Patients Using Chronic Daily Corticosteroids

<table>
<thead>
<tr>
<th>Medical/Surgical Stress</th>
<th>Corticosteroid Dosage DOS*</th>
<th>Postoperative Taper Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor (local anesthesia, &lt; 1 hour) (e.g. inguinal hernia, single tooth extraction, colonoscopy), mild febrile illness, mild, nausea/vomiting, mild diarrhea</td>
<td>25mg or 30-50 mg/m2 po (if able to take po) or IV hydrocortisone (HC) or equivalent</td>
<td>None</td>
</tr>
<tr>
<td>Moderate (e.g. multiple tooth extraction, fracture, pneumonia)</td>
<td>50mg or 50-75 mg/m2 IV hydrocortisone or equivalent</td>
<td>25 mg Q 8 or 50-75 mg/m2/day ÷ q 6 hours X 24 hour. Taper to baseline over 1-2 days.</td>
</tr>
<tr>
<td>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.)</td>
<td>100mg or 100 mg/m2/dose IV hydrocortisone or equivalent</td>
<td>50 mg IV Q 8 or 100 mg/m2/day ÷ q 6 hours X 24-48 hours. Taper to baseline over 1-3 days (continue stress dose if the physical stress (fever or pain) continues).</td>
</tr>
</tbody>
</table>

Table 2: Corticosteroid Stress Dosing

For patients using a high dose, twice-weekly corticosteroid:
- If patients are unable to take their usual corticosteroids by mouth due to nausea, vomiting, or npo status, they should take stress doses intravenously as indicated above.
- During a moderate or major medical or surgical stressor, a cortisol level should be drawn prior to stress dosing.

4. Recommendation for withdrawal of Corticosteroid Therapy:
- It is recommended that patients electing to discontinue the use of corticosteroids do so under the guidance of a
Modification of above protocol:

- Omit monthly AM cortisol and ACTH and perform an ACTH stimulation test in 3 months after discontinuation of corticosteroids
- During this time (3 months before getting ACTH stimulation test), patients will need to take stress dose at the time of stress
- If ACTH stimulation test result is abnormal (peak cortisol <20), patients will need to continue taking stress doses of hydrocortisone at the time of stress. (Patients should have a repeat ACTH stimulation test again in 1-2 months later and families would need to have teaching on this with an endocrine nurse.)

Alternatively, when laboratory tests cannot be carried out:

- Patients who have used corticosteroids for prolonged periods can be considered as having suppression of the HPA axis up

Testing the HPA axis:

- After reaching half the physiological dose (5-6 mg/m2/day of hydrocortisone or 1-1.5 mg/m2/day of prednisone), monthly morning serum cortisol and ACTH should be assayed (may do less frequently), until they reach normal levels.
- When baseline monthly morning serum ACTH and cortisol are normal, discontinue the corticosteroid and carry out therapid ACTH stimulation test (may also be called cosyntropin, tetracosactide or Synacthen tests) monthly until post-stimulation cortisol response is normal (post-stimulus level > 20 mcg/dL). When this point is reached, it can be considered that the HPA axis has recovered.
- It may be appropriate to recheck the rapid ACTH stimulation test after 1 year, to establish continued full recovery of the HPA axis.
to 1 year after discontinuation of corticosteroid therapy and therefore need hydrocortisone stress dose coverage during the time of stress.

Risk factors for adrenal crisis include:19

- Dehydration
- Infection and other physical illness
- Injury to the adrenal or pituitary gland
- Missing usual doses of corticosteroids
- Surgery
- Trauma

Symptoms of adrenal crisis can include any of the following:15

- Abdominal pain
- Hypovolemic shock
- Confusion or coma
- Dehydration
- Dizziness or light-headedness
- Fatigue
- Flank pain
- Headache
- High fever
- Loss of appetite
- Loss of consciousness
- Severe hypotension
- Nausea
- Profound weakness
- Tachycardia
- Tachypnea
- Slow, sluggish movement
- Unusual and excessive sweating on face or palms
- Vomiting

Exams and Tests

While it is appropriate to assess for acute adrenal crisis, this assessment should never delay treatment with a stress dose of hydrocortisone.

Tests that may be ordered to help diagnose acute adrenal crisis include:

- ACTH (cosyntropin) stimulation test
- Cortisol level
- Blood glucose
- Serum potassium
- Serum sodium
- Serum pH

<table>
<thead>
<tr>
<th>Medication</th>
<th>Equivalent doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone</td>
<td>25 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Deflazacort Prednisone or Prednisolone</td>
<td>6 mg</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
</tr>
</tbody>
</table>
Conclusion

This protocol, on how to manage patients with corticosteroid dependence, particularly during periods of stress and how to recognize and prevent an acute adrenal crisis, was named in honor of the late Philip James “PJ” Nicholoff, for his contribution to the global Duchenne community. Despite the tragic loss of PJ’s life, the “PJ Nicholoff Steroid Protocol” is a positive result that will impact the lives of people living with Duchenne and using corticosteroids around the world. We thank PJ and his family for encouraging the development of this resource.


Acknowledgements

In honor of the late Philip James “PJ” Nicholoff, for his contribution to the global Duchenne community.

- Vincent’s Hospital, Indianapolis, IN
- Philip Zeitler, Children’s Hospital Colorado, Aurora, CO
- Sasigarn Bowden, Nationwide Children’s Hospital, Columbus, OH
- Doug Biggar, Holland Bloorview Kids Rehab, Toronto, ON
- Jerry R. Mendell, Nationwide Children’s Hospital, Columbus, OH
- Anne M. Connolly, St. Louis Children’s Hospital, St. Louis, MO

Supporting Organizations

Parent Project Muscular Dystrophy (PPMD)

Parent Project Muscular Dystrophy (PPMD, www.parentprojectmd.org) is the largest nonprofit organization in the United States focused entirely on Duchenne. Started in 1994 by Pat Furlong, PPMD takes a comprehensive approach in the fight against Duchenne—funding research, raising awareness, promoting advocacy, connecting the community, and broadening treatment options. PPMD’s care objectives are to identify gaps in care for people with Duchenne and work toward solutions, and to work with clinicians and other health care professionals across the globe to ensure all Duchenne patients have access to optimal care.

Competing Interests Statement

The Authors have declared that no competing interests exist.

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Acknowledgements

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References


