PJ NICHOLOFF STEROID PROTOCOL

IN PARTNERSHIP WITH

OPTIMIZE DMD
Est. 2023

OPTIMIZING ENDOCRINE AND BONE HEALTH MANAGEMENT IN DUCHENNE MUSCULAR DYSTROPHY

Parent Project Muscular Dystrophy

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PJ NICHOLOFF STEROID PROTOCOL AT-A-GLANCE

Individuals with Duchenne muscular dystrophy who take glucocorticoids (including prednisone, prednisolone, deflazacort, and vamorolone) are at risk of adrenal suppression. This means their bodies cannot produce cortisol normally during times of stress. All patients on steroids need a stress steroid plan for illness, injury, or surgery and must follow a careful tapering schedule when reducing or stopping steroids to prevent potentially life-threatening complications.

Key Things to Remember:

- **Risk of Adrenal Suppression:** Taking high-dose steroids for more than two weeks can suppress your body's ability to produce natural stress hormones, which may lead to adrenal insufficiency.
- **Recognizing Symptoms of Adrenal Insufficiency:** It's important to recognize the signs of adrenal insufficiency while on steroids. Without proper treatment, this condition can lead to a life-threatening emergency called an adrenal crisis.
- **Why a Stress Dosing Plan Matters:** Everyone taking long-term steroids needs a "stress dosing" plan for increasing their steroid dose during times of physical stress such as illness, injury, or surgery.
- **Tapering Steroids Safely:** If you've been on high-dose steroids for more than 2 weeks, the dosage must be reduced slowly over time under the guidance of a medical provider. This gradual reduction in dose is also called a steroid taper. Steroids should never be stopped suddenly.
- **Ongoing Precautions while Tapering/Discontinuing Steroids:** Even while you're tapering or discontinuing steroids, you may still need stress dose steroids during times of illness or injury. This will be needed until your healthcare provider confirms your body is producing normal stress hormone levels again.
- **Changing Steroid Medications:** When switching from one steroid medication to another, your doctor will create a careful plan to prevent adrenal insufficiency.

Key points are based on 6 critical concepts outlined in the PJ Nicholoff Steroid Protocol

1. Individuals taking daily supraphysiologic glucocorticoid doses for greater than two weeks are at high risk for adrenal suppression.
2. Signs and symptoms of adrenal insufficiency are often non-specific and may only develop when the individual is under increased physiologic stress.
3. All individuals on chronic supraphysiologic doses of glucocorticoids must have a stress steroid plan for moderate and severe physiologic stress.
4. A glucocorticoid taper must be implemented when decreasing or discontinuing glucocorticoids in individuals who have been treated with supraphysiologic glucocorticoid doses for greater than 2 weeks
5. Individuals tapering off glucocorticoids (vamorolone, deflazacort, prednisone, or prednisolone) or on physiologic (maintenance) glucocorticoid doses must continue to take stress steroid doses for periods of increased physiologic stress until recovery of the hypothalamic-pituitary-adrenal axis has been confirmed.
6. When transitioning from one glucocorticoid regimen to another, care must be taken to reduce the risk of adrenal insufficiency/adrenal withdrawal.

For more information visit **www.parentprojectmd.org/PJProtocol** or scan here.

About this Document:

This document applies to individuals with muscular dystrophy who are treated with glucocorticoids (GCs) including Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, female manifesting carriers, and X-linked cardiomyopathy (collectively abbreviated as DBMD). For the purposes of this document a GC is defined as a steroid that exerts physiologic actions through the glucocorticoid receptor. Prednisone, prednisolone, deflazacort, and vamorolone are the GCs currently used to treat individuals with DBMD. The standard daily GC regimens used to treat DBMD cause adrenal suppression in most individuals, while intermittent GC dosing regimens may be less likely to cause adrenal suppression. However, because adrenal suppression is life-threatening, all individuals with DBMD on GCs, including intermittent doses, are presumed to be at-risk for adrenal insufficiency and require a preventative management approach.

Adrenal suppression is an iatrogenic, potentially life-threatening condition that is caused by prolonged exposure to supraphysiologic doses of GCs. Supraphysiological doses of GCs are those that exceed the daily production of endogenous cortisol. Proper recognition and management of adrenal suppression can prevent both morbidity and mortality.

The objective of this document is to assist health care providers caring for individuals with DBMD in preventing complications of GC-induced adrenal suppression, including adrenal insufficiency, adrenal crisis, and adrenal withdrawal. For more information on GCs and adrenal suppression, please visit the Parent Project Muscular Dystrophy (PPMD) Steroid Care Page at **www.parentprojectmd.org/steroids**.

This 2025 update provides an approach to the management of adrenal suppression for individuals with DBMD receiving both established (prednisone, prednisolone, deflazacort) and new GCs (vamorolone). Vamorolone, first approved for the treatment of DMD in 2023 in the United States and the European Union, is a novel synthetic GC designed to retain the anti-inflammatory benefits of classic GCs (i.e. prednisolone, prednisone, and deflazacort) with the goal of minimizing side effects by dissociating trans-repression (anti-inflammatory effects) from transactivation (side effects related to gene transcription). Importantly, vamorolone still causes central adrenal suppression through the same mechanism as classic GCs. However, unlike classic GCs, vamorolone is also a mineralocorticoid receptor antagonist, a unique property that may have important implications for clinical care.

This document is informed by evidence-based research and expert clinical opinions [the latter arising from the international Optimizing Endocrine and Bone Health Management in Duchenne Muscular Dystrophy ("OPTIMIZE DMD") Consortium]. It is structured around six critical concepts that together guide current best practices for managing adrenal suppression in individuals with DBMD being treated with GCs:

- **Individuals taking daily supraphysiologic glucocorticoid doses for greater than two weeks are at high risk for adrenal suppression.**
- **Signs and symptoms of adrenal insufficiency are often non-specific and may only develop when the individual is under increased physiologic stress.**

- **All individuals on chronic supraphysiologic doses of glucocorticoids must have a stress steroid plan for moderate and severe physiologic stress.**
- **A glucocorticoid taper must be implemented when decreasing or discontinuing glucocorticoids in individuals who have been treated with supraphysiologic glucocorticoid doses for greater than two weeks.**
- **Individuals tapering off glucocorticoids (vamorolone, deflazacort, prednisone, or prednisolone) or on physiologic (maintenance) glucocorticoid doses must continue to take stress steroid doses for periods of increased physiologic stress until recovery of the hypothalamic-pituitary-adrenal axis has been confirmed.**
- **When transitioning from one glucocorticoid regimen to another, care must be taken to reduce the risk of adrenal insufficiency / adrenal withdrawal.**

Detailed examples for the clinical management of adrenal suppression are also provided. However, it is recognized that substantial clinical practice variability exists around the world. In view of this, the six critical concepts proposed herein are intended to serve as the foundation upon which adrenal suppression management is based. The example clinical strategies are provided to help clinicians implement these principles; they are not intended to supersede existing local adrenal care pathways already in existence. If possible, the inclusion of an endocrinologist on the DBMD care team or as a part of local care pathway development is highly recommended.

Critical concept #1: Individuals taking daily supraphysiologic glucocorticoid doses for greater than two weeks are at high risk for adrenal suppression.

- Under normal circumstances, the hypothalamus secretes corticotropin-releasing hormone, which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH, in turn, signals the adrenal glands to produce cortisol (an endogenous GC) at roughly 8-10 mg/m^2 of body surface area (BSA) per day in enteral hydrocortisone equivalents (also known as maintenance production).
- During physiologic stress (illness, trauma, or surgery), cortisol secretion increases significantly (to triple maintenance production or more).
- All standard daily GC regimens used to treat DBMD (**Table 1**) can suppress the hypothalamic-pituitary-adrenal (HPA) axis, causing iatrogenic adrenal suppression, a form of adrenal insufficiency that can result in significant morbidity and even death due to a lack of cortisol during times of increased physiologic stress.
- Without appropriate stress steroid dosing, adrenal suppression may lead to adrenal insufficiency, which has the potential for a life-threatening adrenal crisis characterized by vomiting, altered mental status, cardiovascular collapse, and/or hypoglycemia during times of moderate to severe physiologic stress.

Table 1. Starting glucocorticoid doses commonly used to treat Duchenne muscular dystrophy and other dystrophinopathies (DBMD)

Gluccocorticoid	DBMD treatment doses
Prednisolone	0.75 mg/kg/day (typical max dose 40 mg)[1]
Prednisone	0.75 mg/kg/day (typical max dose 40 mg)[1]
Deflazacort	0.9 mg/kg/day (typical max dose 36 mg)[1]
Vamorolone	6 mg/kg/day[2] (max dose 300 mg USA, 240 mg EU)

[1] Maximum dose not specified in prescribing information and may vary on a case-by-case basis at the discretion of the treating clinician
[2] Recommended dose for moderate hepatic impairment is 2 mg/kg/day (max dose 100 mg/day); moderate hepatic impairment increases vamorolone exposure. There are no data to guide vamorolone dosing in individuals with severe hepatic impairment.
Abbreviations: DBMD, Duchenne and Becker Muscular Dystrophy and other dystrophinopathy; EU, European Union; max, maximum ; USA, United States of America.

Critical concept #2: Signs and symptoms of adrenal insufficiency are often non-specific and may only develop when the individual is under increased physiologic stress.

- All individuals must be educated about the signs and symptoms of adrenal insufficiency BEFORE or AT THE TIME of starting GC therapy, **Table 2**. This education should be reinforced annually, at a minimum, for as long as GC therapy continues.
- All individuals treated with GCs must be educated to never stop or hold GC doses, as this could precipitate symptoms of adrenal insufficiency and an adrenal crisis. A missed dose can be administered at any time during the day it was scheduled to be taken.
- Adrenal withdrawal is a different entity from adrenal insufficiency. The symptoms of adrenal withdrawal may mimic adrenal insufficiency though they are not life threatening. Symptoms of adrenal withdrawal may occur during a GC taper even when on high GC doses, or when transitioning from one GC or GC regimen to another.

Table 2: Signs and symptoms of glucocorticoid (GC) induced adrenal insufficiency

Symptoms of GC-induced adrenal insufficiency[1]	Signs of GC-induced adrenal insufficiency[1]
Anorexia	Hypotension
Nausea /vomiting	Hypoglycemia
Malaise	Tachycardia or Bradycardia
Weakness or fatigue	Fever[2]
Headache	
Abdominal pain	
Myalgia/arthralgia	
Psychiatric symptoms (confusion, delirium, disorientation)	
Loss of motor skills (out of keeping with natural progression)	

[1] Symptoms of adrenal withdrawal may mimic symptoms of adrenal insufficiency. Note that not all symptoms and/or signs are always present. Hypotension and hypoglycemia typically do not occur with adrenal withdrawal.

[2] Fever is an uncommon sign of adrenal insufficiency. The source of fever should always be investigated and treated, as appropriate

Critical concept #3: All individuals on chronic supraphysiologic doses of glucocorticoids must have a stress steroid plan for moderate and severe physiologic stress.

- Supra-physiological doses of GCs are those that exceed the daily production of endogenous cortisol (maintenance), and only those with mineralocorticoid receptor agonist properties and longer duration of action can be used for stress coverage, **Table 3**.
- Extra GCs (referred to as stress steroid doses) must be given during times of increased physiologic stress including illness, accident/injury, or surgery, to prevent life-threatening consequences. Examples of moderate and severe physiologic stress are provided in **Table 4**. Example stress steroid regimens are provided in **Tables 5 and 6**.

Table 3. Maintenance doses and stress dosing considerations for glucocorticoids in Duchenne muscular dystrophy and other dystrophinopathies

Gluccocorticoid	Used for DBMD Treatment	Maintenance dose[1]	Half-life (hours)[2]	Gluccocortiod receptor activity	Mineralocorticoid receptor activity	Appropriate for stress coverage[3]
Hydrocortisone	NO	8-10 mg/m^2/day	3	Agonist	Agonist	YES
Prednisone	YES	2-3 mg/m^2/day	6.2	Agonist	Agonist	YES
Prednisolone	YES	2-3 mg/m^2/day	6.2	Agonist	Agonist	YES
Deflazacort	YES	2.6 mg/m^2/day[4]	1.1 to 1.9	Agonist	Weak agonist	UNKNOWN[5]
Vamorolone	YES	Unknown	2	Agonist	Antagonist	NO

[1] Expressed as mg/m2 of body surface area (BSA)/day. There are multiple equations for calculation of BSA, the equation used in the local electronic health record or practice is encouraged. BSA can also be estimated from weight alone: (weight (kg) × 4) + 7/(weight (kg) + 90)
[2] Clinically a drug is considered to be eliminated from the body after 4-5 half-lives
[3] See **Tables 5 and 6** for stress dosing details
[4] Estimates based on historically accepted conversion factors and should be considered a guide only. Deflazacort is not recommended for maintenance replacement.
[5] Insufficient data to inform stress dose or frequency. Use with caution.
Abbreviations: DBMD, Duchenne and Becker Muscular Dystrophy and other dystrophinopathy

Table 4: Indications and examples for moderate and severe stress steroid dose administration in addition to regular glucocorticoid regimen

Situation	Stress Steroid Dose Recommendations[1,2] **See Tables 5 and 6 for Doses**	Duration of Stress Dose
Minor Illness: • Examples: mild cold/runny nose without fever; feels well enough to attend school, work or other activities	No change	Not applicable
Minor Injury: • Examples: finger fracture that does not break skin, abrasions, bruises; minimal or no pain is a good barometer of the need for stress dosing	No change	Not applicable
Moderate Illness: • Illnesses that would keep a child from going to school or an adult from going to work • Examples include fever, severe cold with fatigue, mild diarrhea, mild vomiting (and able to keep enteral medication down)	Hydrocortisone every 6-8 hours enterally or Prednisone/prednisolone every 12 hours enterally	Until illness resolved + 24 hours
Moderate Injury: • Example: arm or leg fracture or acute symptomatic vertebral fracture that does not break skin	Hydrocortisone every 6-8 hours enterally or Prednisone/prednisolone every 12 hours enterally	Until acute pain resolved and injury has been treated

Severe Illness • Persistent vomiting and unable to keep stress steroid medication down • Severe diarrhea that might adversely affect absorption • Decreased level of consciousness or difficulty rousing from sleep	Hydrocortisone IM and Go to emergency department and/ or call emergency services	Variable, individualized by course
Severe Injury or Trauma: • Examples: motor vehicle accident, fracture that breaks skin, any injury resulting in loss of consciousness	Hydrocortisone IM and Go to emergency department and/ or call emergency services	Variable, individualized by course
Minor Surgery: • Examples: procedures with local anesthesia or mild to moderate sedation that do not result in loss of consciousness	Consider: Hydrocortisone every 6-8 hours enterally or Prednisone/prednisolone every 12 hours enterally Decision to stress dose is informed by complexity of procedure and patient history	24 hours post procedure
Major Surgery: • Procedures under general anesthesia	Administer hydrocortisone IV prior to induction of general anesthesia and Provide stress steroid plan to anesthesia team Ongoing IV GCs required if patient unable to resume enteral GC regimen following the procedure	Variable, individualized by course
Bisphosphonate infusions: • Recommended for signs/symptoms of acute phase response (APR; fever, nausea, myalgia, bone pain) • Consider empiric stress dosing for first infusions where risk of APR is greatest. • Need for empiric stress dosing for subsequent infusions can be informed by initial response; should always be given if symptoms of APR develop	Hydrocortisone every 6-8 hours enterally or Prednisone/prednisolone every 12 hours enterally	Until signs and symptoms of APR have passed + 24 hours

[1] Hydrocortisone is given in addition to the usual DBMD deflazacort or vamorolone treatment dose. The DBMD treatment doses of prednisone/prednisolone typically exceed what is needed for stress steroid dosing. In these cases, the usual DBMD prednisone/prednisolone dose can be divided into two equal doses given 12 hours apart. There is insufficient data to inform optimal dose and frequency of deflazacort for stress dosing.
[2] Institution-specific practices should be informed in collaboration with a local expert (endocrinologist), if available
Abbreviations: IM, intra-muscular

- All individuals must have a stress steroid plan for at-home and in-hospital use BEFORE or AT THE TIME of starting GCs for the treatment of DBMD. This includes a plan for moderate (**Table 5**) and severe (**Table 6**) physiologic stress.
- Hydrocortisone, prednisone and prednisolone are acceptable for stress dosing because they are agonists for both the glucocorticoid and mineralocorticoid receptors, **Table 3**.
- Hydrocortisone is dosed every 6-8 hourly when used for moderate stress dosing. It is given in addition to the regular DBMD GC treatment dose.

- Prednisone and prednisolone are more potent and longer acting GCs that are given every 12 hours when used for moderate stress dosing. In most cases, the DBMD treatment doses of prednisone/prednisolone exceed the doses required for stress dosing. In these cases, the regular DBMD prednisone/prednisolone dose can be split into two equal doses given 12 hours apart.
- ***It is unknown if deflazacort is appropriate for stress dosing.*** Deflazacort has a shorter half-life than hydrocortisone and prednisone/prednisolone. The optimal dose and frequency for stress dosing with deflazacort is not known.
- ***Vamorolone cannot be used for stress dosing*** because it is a mineralocorticoid receptor antagonist and hypothetically could exacerbate risk of hypotension during an adrenal crisis.
- Intramuscular (IM) or intravenous (IV) hydrocortisone is required for the treatment of severe physiologic stress and in cases of persistent vomiting or severe diarrhea, **Table 6**.
- Individuals should be encouraged to wear a medical identification bracelet or necklace that states they are steroid-dependent. They should also carry a physical and/or electronic wallet card that describes their stress steroid plan.
- Adrenal insufficiency should be flagged in the individual's electronic health record and there should be clear documentation of the stress steroid plan to guide any physician or health care team.

Moderate Stress Steroid Dosing:

- Enteral hydrocortisone or prednisone/prednisolone must be given during periods of moderate physiologic stress as outlined in **Table 4**.
- Enteral stress doses with hydrocortisone or prednisone/prednisolone can be based on BSA (m2) or measured weight (kg). BSA is preferred, as it is more precise, but not always practical. Suggested stress steroid doses are provided in **Table 5** by BSA and by weight.
- If DBMD treatment doses of prednisone/prednisolone exceed what is needed for stress steroid dosing (**Table 5**), the usual DBMD prednisone/prednisolone dose can be divided into two equal doses given 12 hours apart.

Table 5: Moderate stress steroid doses according to body surface area (BSA)[2] or weight (enteral, by mouth or gastro-intestinal tube)[1]

BSA based dosing		
	Hydrocortisone	**Prednisone or Prednisolone[2]**
All individuals	30 -50 mg/m^2 /day divided every 6-8 hours Max dose 15 mg every 6-8 hours	8-12 mg/m^2/day divided every 12 hours Max dose 7.5 mg every 12 hours[3]
Weight based dosing		
Body Weight	**Hydrocortisone**	**Prednisone or Prednisolone[2]**
10 to 25 kg	5 mg every 6-8 hours	2.5 mg every 12 hours
26 to 50 kg	10 mg every 6-8 hours	5 mg every 12 hours
>50 kg	15 mg every 6-8 hours	7.5 mg every 12 hours

[1] Choice of hydrocortisone vs prednisone vs prednisolone is per provider and patient/family preference. If a liquid preparation is needed, check with local pharmacy to confirm shelf stability and advise individual/family on the frequency of refills needed.
[2] As long as the DBMD treatment doses of prednisone/prednisolone exceed what is needed for stress steroid dosing the usual DBMD prednisone/prednisolone dose can simply be divided into two equal doses given 12 hours apart
[3] Max dose applicable only when given in addition to usual DBMD steroid dose.

Severe Stress Steroid Dosing:

- Intramuscular (IM) or intravenous (IV) hydrocortisone is required during periods of severe physiologic stress as outlined in **Table 4**.
- The standard initial severe stress dose is 100 mg/m2 of BSA (max 100 mg), **Table 6**. Age-based dosing is appropriate if BSA is unknown.
- Ongoing IV hydrocortisone at doses of 50-100 mg/m2/day divided every 4-6 hours may be required for ongoing physiologic stress or inability to tolerate enteral GC dosing.
- Continuous hydrocortisone infusions can be considered instead of intermittent boluses, per institutional practice, **Table 7.**
- If critically ill, blood glucose and blood pressure should be assessed. Hypoglycemia and/or hypotension should be corrected per standard clinical interventions.

Table 6: Severe stress steroid doses according to body surface area (BSA) or age[1]

BSA based dosing	
	IM or IV hydrocortisone
All individuals	100 mg/m^2 (maximum dose of 100 mg)
Age based dosing	
Age	**IM or IV hydrocortisone**
< 1 year	25 mg
1-5 years	50 mg
≥ 6 years	100 mg

[1] Initial dose provided. Ongoing IV hydrocortisone at doses of 50-100 mg/m2/day divided every 4-6 hours may be required for ongoing physiologic stress or inability to tolerate enteral GCs.
Abbreviations: IM, intramuscular; IV, Intravenous

Table 7: Continuous IV hydrocortisone infusion rates based on measured weight as an alternative to intermittent doses for severe stress

Weight	Total dose in 24 hours	Hydrocortisone infusion rate[1]
≤ 10kg	24 mg	1 ml/hr
10.1 to 20kg	48 mg	2 ml/hr
20.1 to 40kg	96 mg	4 ml/hr
40.1 to 70kg	144 mg	6 ml/hr
Over 70kg	192 mg	8 ml/hr

[1] Hydrocortisone infusion for IV use prepared as 50 mg hydrocortisone in 50 mL 0.9% sodium chloride (1 mg/mL)
Abbreviations: IM, intramuscular; IV, intravenous

Critical concept #4: A glucocorticoid taper must be implemented when decreasing or discontinuing glucocorticoids in individuals who have been treated with supraphysiologic glucocorticoid doses for greater than 2 weeks

- Rapid reduction or abrupt withdrawal of GCs can cause adrenal withdrawal, adrenal insufficiency, or adrenal crisis.
- A gradual taper in the GC dose before discontinuation may reduce the risk of adrenal insufficiency, although it does not completely prevent this risk.
- Individuals must be re-educated about the signs and symptoms of adrenal insufficiency including adrenal withdrawal and adrenal crisis prior to starting a GC taper.
- Stress steroid doses must still be given during times of increased physiologic stress during the GC taper and until recovery of the HPA axis has been confirmed by morning cortisol or ACTH stimulation testing, **Table 8, Step 3**

Approach to Glucocorticoid Taper

There is insufficient evidence to support a specific approach to GC tapering. Institution or other regulatory body-specific GC tapering protocols may exist and should be consulted, if available, to comply with local regulations and clinical practice.

- In the absence of local guidance, an example of a GC tapering protocol is provided in **Table 8**.
    - In this example, GCs are first tapered from treatment to "triple-maintenance" doses (i.e. three times maintenance dose) as outlined in **Table 8 and Table 9**.
        - GCs are tapered to triple maintenance to provide stress steroid coverage pending involvement of an endocrinologist who can manage the tapering process, if available
        - Typically, the taper to "triple maintenance" doses is managed by the treating neuromuscular specialist (with advice from endocrinologist, where appropriate) and may need to be individualized based upon the specific clinical scenario.
        - The taper may need to proceed more quickly for individuals with intolerable symptoms of GC toxicity such as mood disturbance, increased intraocular pressure, or excessive weight gain.
        - The taper may need to proceed more slowly if muscle weakness or other symptoms of DBMD worsen as the GC doses are lowered, or if the individual does not tolerate the taper otherwise.
        - For individuals who feel unwell during a GC taper, they should return to the last dose and frequency at which they felt well, remain on this dose until they feel well again, and then resume the taper at a slower rate.
- Once GCs have been tapered to "triple maintenance" dose, an endocrinologist should be consulted, if available, to guide further management including tapering to a "maintenance" dose (**Tables 9 and 10**) and evaluation for HPA axis recovery.
    - If an endocrinologist is not available, a possible approach for tapering from "triple maintenance" to "maintenance" is provided in Step 2 of **Table 8**
- Significant variability in clinical practice exists for evaluating the HPA axis.
    - Acceptable approaches include assessing morning blood cortisol OR performing an ACTH stimulation test after holding all GCs for at least 24 hours, **Step 3 of Table 8**. There is insufficient evidence to support one approach over another.
- ***The stress steroid dose plan must continue until recovery of the HPA axis has been confirmed.***

Table 8: An example approach for how to taper glucocorticoids (GCs) and test for recovery of the hypothalamic pituitary adrenal axis (HPA)*

***Consult local institution or endocrinologist to determine if an institutionally approved GC taper guideline exists**

Step 1: Tapering GCs from DBMD treatment dose to "triple maintenance" dose[1]	

• Typically overseen by the treating neuromuscular provider
• Goals:
  • Avoid possible deleterious rebound effects of abruptly stopping GCs on muscle function
  • Avoid symptoms of adrenal withdrawal[2]
• Stress dose steroids are required during periods of increased physiologic stress[3]
• Additional considerations:
  • Faster tapers may be required for some patients based upon severity of initial symptoms of GC toxicity
  • Consider slowing taper if symptoms of adrenal withdrawal or worsening muscle function
	Possible approach to tapering GCs from treatment to triple maintenance
	
	Prednisone/prednisolone
	• Decrease dose by 2.5-5 mg every 1-2 weeks until "triple maintenance" dose (**Table 9**)
	
	Deflazacort
	• Decrease dose by 3-6 mg every 1-2 weeks until weight based "triple maintenance" dose (**Table 9**)
	
	Vamorolone
	Depending on individual/caregiver and health care provider preference:
	• Start maintenance doses of hydrocortisone, prednisone, or prednisolone (**Table 10 or 11**) in addition to vamorolone, **AND THEN**
	• Decrease dose of vamorolone by 1 mg/kg/day every 1-2 weeks until tapered completely off vamorolone
	or
	• If need to stop vamorolone as soon as possible, switch directly from vamorolone to weight based triple maintenance dose of a classic GC (**Table 9**)

Step 2: Tapering GCs from "triple maintenance" to "maintenance" dose[1]	

• Typically overseen by an endocrinologist, if available
• Goals:
  • Avoid symptoms of adrenal withdrawal[2]
  • Allow recovery of endogenous cortisol production
• Stress dose steroids are required during periods of increased physiologic stress[3]
• Additional considerations:
  • Faster tapers may be required for some patients based upon severity of initial symptoms of GC toxicity
  • Consider slowing taper if symptoms of adrenal withdrawal or worsening muscle function
	Possible approach to tapering GCs from "triple maintenance" to "maintenance" doses
	
	Prednisone or prednisolone
	Decrease prednisone or prednisolone by 1-5 mg/day, every 4-7 days, until maintenance doses are reached (**Table 10 or 11**). Speed of taper, magnitude and frequency of dose reduction are guided by the duration of prior GC exposure:
	• Duration of GC use < 2 weeks no taper needed
	• Duration of GC use 2 weeks to 3 months: taper over 1-2 weeks
	• Duration of GC use 3-6 months: taper over 2 weeks
	• Duration of GC use > 6 months: taper over 2-4 weeks
	
	Deflazacort
	• Switch to "triple maintenance dose" of prednisone, prednisolone, or hydrocortisone (**Table 9**)
	• Prednisone/prednisolone: decrease dose by 1-5 mg/day, every 4-7 days until maintenance doses are reached (**Table 10 or 11**)
	• Hydrocortisone: decrease dose by 2.5-5 mg/day, every 4-7 days until maintenance doses are reached (**Table 10 or 11**)
	• Speed of taper, magnitude and frequency of dose reduction are guided by the duration of prior GC exposure:
	  • Duration of GC use < 2 weeks: no taper needed
	  • Duration of GC use 2 weeks to 3 months: taper over 1-2 weeks
	  • Duration of GC use 3-6 months: taper over 2 weeks
	  • Duration of GC use > 6 months: taper over 2-4 weeks
	
	Vamorolone
	As described in Step 1 above

<table>
<tr><th colspan="2">Step 3: Testing for recovery of hypothalamic pituitary adrenal (HPA) axis</th></tr>
<tr><td rowspan="2">• Typically overseen by an endocrinologist, if available
• Evaluation for recovery of the HPA axis is typically performed 1-3 months after transitioning to maintenance GC doses,4 either with morning blood cortisol or low or standard dose ACTH stimulation test[5]
  • Assessments should be performed at least 24 hours after holding GC dose
  • Maintenance doses should be restarted after the test and continue until results are reviewed and communicated</td><td>Guide to interpretation of morning (8:00 - 9:00 AM) cortisol or ACTH stimulation test
• Interpretation of 8:00 AM morning cortisol[6]
• <150 nmol/L (5.0 µg/dL) or lower threshold for local assay: HPA axis likely remains suppressed.
  • Continue or consider restarting maintenance GC
  • Continue stress steroid plan
  • Retest in 1-6 months
• Between 150 nmol/L (5.0 µg/dL) and 300 nmol/L (10.0 µg/dL) or upper threshold for local assay: HPA axis likely partially recovered
  • Cntinue or consider restarting maintenance GCs if symptomatic
  • Continue stress steroid plan
  • Retest in 1-6 months or proceed to ACTH stimulation testing
• ≥ 300 nmol/L (10 µg/dL) or upper threshold for local assay: HPA axis likely recovered
  • Stop or do not restart maintenance GCs
  • Safe to stop stress steroids in most cases. Consider ACTH stimulation testing or continue stress steroid doses x 6-12 months, based upon clinical judgement</td></tr>
<tr><td>Interpretation of 30- or 60-minute response to low or standard dose ACTH stimulation testing[6]
• < 400 nmol/L (14.5 mcg/dL) or upper threshold for local assay: HPA axis likely not fully recovered
  • Continue or consider restarting maintenance GC dosing
  • Continue stress steroids
  • Retest in 1-6 months
• ≥ 400 nmol/L (14.5 mcg/dL) or threshold from local center: HPA axis likely fully recovered
  • Safe to stop maintenance GCs
  • Stress steroids no longer needed</td></tr>
</table>

[1] Triple maintenance doses are provided in **Table 9**, maintenance doses are provided in **Tables 10 and 11**
[2] Symptoms of adrenal withdrawal may include fatigue, weakness, anorexia, nausea, headache, **Table 2**
[3] Indications for stress dosing in **Table 4**. Standard stress doses are 30-50 mg/m2/day (moderate stress) and 100 mg/m2/day (severe stress) of hydrocortisone equivalents, **Tables 5 & 6**
[4] Some endocrinologists will provide instructions for an additional GC taper below maintenance GC levels to be done prior to assessing HPA axis
[5] Discussion of standard vs low dose ACTH stimulation test is beyond the scope of this document, choice of test should be per local practice
[6] Exact cortisol values are dependent on local assay used – consult with local endocrinologist or lab pathologist
Abbreviations: GC, glucocorticoid; HPA, hypothalamic pituitary adrenal

Table 9: Suggested weight-based "triple maintenance" doses to be used when tapering glucocorticoids

Weight	Prednisone or prednisolone[1]	Deflazacort[1]	Hydrocortisone[2]	Vamorolone[3]
10-25 kg	5 mg enteral daily	6 mg enteral daily	20 mg enteral daily	Not Applicable
26-50 kg	10 mg enteral daily	12 mg enteral daily	40 mg enteral daily	
51-90 kg	15 mg enteral daily	18 mg enteral daily	60 mg enteral daily	

[1] divided into 2 doses per day
[2] divided into 3-4 doses per day
[3] see **Table 8** for guidance on tapering vamorolone

Table 10: Maintenance glucocorticoid doses by body surface area

Glucocorticoid	Physiologic (maintenance)
Hydrocortisone[1]	8-10 mg/m^2/day
Prednisolone[2]	2-3 mg/m^2/day
Prednisone[2]	2-3 mg/m^2/day
Deflazacort[3]	2.6 mg/m^2/day
Vamorolone	Unknown

[1]Total hydrocortisone dose typically divided into 3 doses per day; dividing into 2 doses per day is also acceptable
[2] Total prednisone/prednisolone is typically divided into 2 doses per day; giving as a single daily dose is also acceptable
[3] Deflazacort is not typically used solely for maintenance replacement. Maintenance dosing frequency is not known

Table 11: Maintenance glucocorticoid doses by body weight

Body Weight	Hydrocortisone[1]	Prednisone/Prednisolone[2]
18-25.9 kg (BSA 0.74-0.92 m^2)	Total 7.5 mg/day, divided as 2.5 mg - 2.5 mg - 2.5 mg	Total 2 mg/day, divided as 1 mg - 1 mg
26-38.9 kg (BSA 0.95-1.2 m^2)	Total 10 mg/day, divided as 5 mg - 2.5 mg - 2.5 mg	Total 2 mg/day, divded as 1 mg - 1 mg
39-53.9 kg (BSA 1.3-1.5 m^2)	Total 12.5 mg/day, divided as 5 mg - 5 mg - 2.5 mg	Total 3 mg/day, divided as 2 mg - 1 mg
54-69.9 kg (BSA 1.6-1.8 m^2)	Total 15 mg/day, divided as 5 mg - 5 mg - 5 mg	Total 4 mg/day, divided as 2 mg - 2 mg
>70 kg (BSA >1.9 m^2)	Total 17.5 mg/day, divided as 7.5 mg - 5 mg - 5 mg	Total 4 mg/day, divided as 2 mg - 2 mg

[1] Total hydrocortisone dose typically divided into 3 doses per day; dividing into 2 doses per day is also acceptable
[2] Total prednisone/prednisolone is typically divided into 2 doses per day; giving as a single daily dose is also acceptable

Critical concept #5: Individuals tapering off glucocorticoids (vamorolone, deflazacort, prednisone, or prednisolone) or on physiologic (maintenance) glucocorticoid doses must continue to take stress steroid doses for periods of increased physiologic stress until recovery of the hypothalamic-pituitary-adrenal axis has been confirmed

- Individuals must a have supply of enteral hydrocortisone, prednisone, or prednisolone and IM hydrocortisone and follow stress steroid plans for moderate and severe physiologic stress until recovery of the HPA axis has been confirmed.
- It can take 6-12 months or longer for the HPA axis to recover.

Critical concept #6: When transitioning from one glucocorticoid regimen to another, care must be taken to reduce the risk of adrenal insufficiency / adrenal withdrawal

- Individuals should be transitioned directly to the standard recommended DBMD treatment dose (**Table 1**), if possible, when transitioning from one GC to another. The dose can then be tapered if a lower dose is desired.

- Individuals with DBMD, and their caregivers, should be re-educated about the signs and symptoms of adrenal insufficiency including adrenal withdrawal and adrenal crisis prior to transitioning GC regimens.
    - If signs of adrenal withdrawal or adrenal insufficiency occur during the transition, individuals must contact the treating physician to discuss increasing the GC dose or adding stress steroids, as indicated.
- The risk of adrenal suppression for intermittent DBMD GC treatment regimens (e.g., "10 days on, 10 days off" or "weekend only") is likely less than daily GC regimens. However, some risk may exist, especially during the transition from daily to intermittent GC regimens.
- A local (or distant [i.e. telemedicine]) endocrinologist should be consulted to assist with transitioning from a daily to an intermittent GC regimen, if available
- Vamorolone should not be used for intermittent or weekend-only GC treatment.
- Example approaches for managing GC transitions are shown in **Table 12**:

Table 12. Example approaches to transitioning individuals from one glucocorticoid or glucocorticoid regimen to another

Navigate to the desired scenario for GC transition. The proposed management offers a potential approach to making the transition from one GC or GC regimen to another. The recommended approach when transitioning GC regimens is to initiate the new GC at the standard DBMD treatment dose (as outlined in the prescribing information) and then titrate to desired dose, if needed. During a GC taper, if the individual experiences symptoms of adrenal insufficiency, adrenal withdrawal, or muscle weakness, go back to the previous dose at which the individual felt well, continue this dose until the individual feels well again, and then consider a more gradual taper.

- In cases where individuals cannot transition to the full recommended DBMD treatment dose, consult with a local (or distant [i.e. telemedicine]) endocrinologist for assistance with transition plan, if available - additional GCs may be needed temporarily during the transition.
- In all cases ensure to re-educate individual/caregivers about signs/symptoms of adrenal insufficiency and the stress steroid plan.

Scenario	Proposed management
Daily prednisone, prednisolone or deflazacort to vamorolone dose of 6 mg/kg/day (recommended approach)	• No tapering needed; can switch directly to vamorolone 6 mg/kg/day • Ensure the first day of vamorolone dosing directly follows the last day of prednisone, prednisolone, or deflazacort such that no doses are missed
Daily prednisone, prednisolone or deflazacort to vamorolone dose < 6 mg/kg/day (or < maximum dose)	• In addition to desired vamorolone dose, initiate hydrocortisone, prednisone, or prednisolone at maintenance dose (**Table 10 or 11**) • Suggest continuing for 4 weeks after the transition to facilitate a smooth change from one to the other, and then stop • If symptoms of adrenal withdrawal develop, initiate moderate stress dosing (**Table 5**) followed by a gradual taper back to maintenance dose

Vamorolone to prednisone, prednisolone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day (recommended approach)	• No tapering needed; can switch directly to prednisone or prednisolone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day • Ensure the first day of prednisone, prednisolone, or deflazacort dosing directly follows the last day of vamorolone dosing such that no doses are missed.
Vamorolone to prednisone/prednisolone doses < 0.75 mg/kg/day or deflazacort doses < 0.9 mg/kg/day	• If desired prednisone, prednisolone or deflazacort treatment dose exceeds triple maintenance dose (**Table 9**) then no tapering needed. Switch directly to desired dose. • If desired prednisone, prednisolone or deflazacort dose is less than triple maintenance (**Table 9**), switch to triple maintenance dose of prednisone, prednisolone or deflazacort (**Table 9**) and then taper by 2.5-5 mg every 2 weeks until desired dose is reached
Daily prednisone, prednisolone, deflazacort, or vamorolone to intermittent prednisone, prednisolone or deflazacort doses including 10 days on 10 days off	• Start maintenance prednisone, prednisolone, or hydrocortisone (**Tables 10 and 11**) on days when not receiving intermittent treatment dose. Suggest continuing for 4 weeks and then stopping. If symptoms of adrenal withdrawal develop, restart maintenance dosing and consider a longer duration of treatment or a taper off maintenance doses • If intermittent prednisone, prednisolone or deflazacort treatment day dose exceeds triple maintenance dose (**Table 9**) then no tapering needed. Switch directly to desired intermittent prednisone, prednisolone or deflazacort treatment day dose • If desired intermittent prednisone, prednisolone or deflazacort treatment day dose is less than triple maintenance (**Table 9**), switch to triple maintenance dose of prednisone, prednisolone of deflazacort on treatment days (**Table 9**) and then taper by 2.5-6 mg every 2 weeks until desired intermittent treatment day dose is reached • Ensure the first day of prednisone, prednisolone, or deflazacort treatment dosing directly follows the last day of daily treatment dosing such that no doses are missed • Re-educate individual/caregivers about signs/symptoms of adrenal insufficiency and stress-steroid plan • Consult endocrinology, if available, and consider testing of HPA axis after 1-6 months (**Table 8, Step 3**), to determine if routine ongoing stress steroid coverage is needed
Daily prednisone, prednisolone, deflazacort, or vamorolone to weekend-only prednisone, prednisolone, or deflazacort doses	• Start maintenance prednisone, prednisolone, or hydrocortisone (**Tables 10 and 11**) on days when not receiving intermittent treatment dose. Suggest continuing for 4 weeks and then stopping. If symptoms of adrenal withdrawal develop, restart maintenance dosing and consider a longer duration of treatment or a taper off maintenance doses • If weekend-only prednisone, prednisolone or deflazacort treatment day dose exceeds triple maintenance dose (**Table 9**), then start weekend-only prednisone, prednisolone or deflazacort dose directly • If weekend-only prednisone, prednisolone or deflazacort treatment day dose is less than triple maintenance dose (**Table 9**), then switch to triple maintenance dose of prednisone, prednisolone or deflazacort (**Table 9**) and then taper by 2.5-6 mg every 2 weeks until desired weekend-only treatment day dose is reached • Ensure that the first day of weekend-only prednisone, prednisolone or deflazacort dosing directly follows the last day of daily treatment dosing such that no doses are missed • Re-educate individual/caregivers about signs/symptoms of adrenal insufficiency and stress-steroid plan • Consult endocrinology, if available, and consider testing of HPA axis after 1-6 months (**Table 8, Step 3**), to determine if routine ongoing stress steroid coverage is needed

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Key References and Additional Resources:
General information on the managemnt of adrenal insufficiency

Ahmet A, Mokashi A, Goldbloom EB, Huot C, et al. Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children. BMJ Paediatr Open. 2019;3(1):e000569.

Bornstein SR, Allolio BA, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. JCEM.2016;101(2):364-89.

Mushtaq T, Ali SR, Boulos N, Boyle R, et al. Emergency and perioperative management of adrenal insufficiency in children and young people: British Society for Paediatric Endocrinology and Diabetes consensus guidance. Arch Dis Child. 2023;108(11):871-8.

Shulman DI, Palmert MR, Kemp SF, et al. Adrenal insufficiency: still a cause of morbidity and death in childhoodPediatrics. 2007;119(2): e484-94.

Information on glucocorticoid equivalency

Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function Am J Med. 1977;63(2):200-7

Parente L. Deflazacort: therapeutic index, relative potency and equivalent doses versus other corticosteroidsBMC Pharmacol Toxicol. 2017;18(1):1

Punthakee Z, Legault L, Polychronakos C. Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency J Pediatr 2003;143:402–5. 73

Information on vamorolone

European Medicines Agency Vamorolone Prescribing Information: https://www.ema.europa.eu/en/medicines/human/EPAR/agamree Last accessed 21 March 2025

FDA Vamorolone Prescribing Information In: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215239s000lbl.pdf Last accessed 21 March 2025

Ahmet A, Tobin R, Dang UJ, et al: Adrenal suppression from vamorolone and prednisone in Duchenne muscular dystrophy: results from the phase 2b clinical trial. JCEM 2025, 110(2):334-344.

Dang UJ, Damsker JM, Guglieri M, et al: Efficacy and Safety of Vamorolone Over 48 Weeks in Boys With Duchenne Muscular Dystrophy: A Randomized Controlled Trial. Neurology 2024, 102(5):e208112

Guglieri M, Clemens PR, Perlman SJ, et al: Efficacy and Safety of Vamorolone vs Placebo and Prednisone Among Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA Neurol 2022, 79(10):1005-1014.

Mah JK, Clemefns PR, Guglieri M, et al: Efficacy and Safety of Vamorolone in Duchenne Muscular Dystrophy: A 30-Month Nonrandomized Controlled Open-Label Extension Trial. JAMA Netw Open 2022, 5(1):e2144178.

Mavroudis PD, van den Anker J, Conklin LS, et al. Population Pharmacokinetics of Vamorolone (VBP15) in Healthy Men and Boys With Duchenne Muscular Dystrophy. J Clin Pharmacol. 2019,59(7):979-988.

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