



# Prevention and management of glucocorticoid-induced side effects: A comprehensive review

## Gastrointestinal and endocrinologic side effects

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### Learning objectives

After completing this learning activity, participants should be able to describe important gastrointestinal and endocrinologic side effects of glucocorticoid use and devise strategies for preventing and diagnosing these complications in patients taking glucocorticoids.

### Disclosures

#### Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Part 2 of this 4-part continuing medical education series continues with a discussion of the prevention and management of gastrointestinal side effects associated with corticosteroid use, including peptic ulcer disease, gastrointestinal bleeding, and pancreatitis, followed by a review of corticosteroid-related endocrinologic side effects, such as diabetes, adrenal suppression, and Cushing syndrome. (*J Am Acad Dermatol* 2017;76:11-6.)

**Key words:** adrenal suppression; Cushing syndrome; diabetes; gastrointestinal bleeding; glucocorticoids; peptic ulcer disease; side effects; steroids.

## GASTROINTESTINAL SIDE EFFECTS

### Key points

- **Glucocorticoid therapy with concomitant nonsteroidal antiinflammatory drug use increases the risk of peptic ulcer disease and gastrointestinal bleeding**

- **Proton pump inhibitors are an effective means of gastrointestinal prophylaxis, but they are not without side effects**

Gastrointestinal (GI) side effects linked to glucocorticoid use include peptic ulcer disease (PUD), GI bleeding, and pancreatitis.

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Please note that infectious and other complications of steroid use will be discussed in the third and fourth installments of this Continuing Medical Education feature in the February 2017 issue of the *JAAD*.

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### Peptic ulcer disease

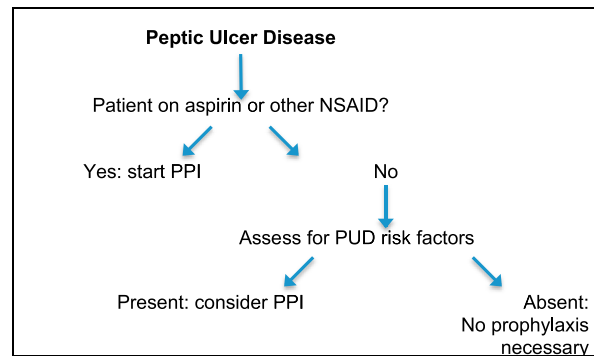
There is conflicting evidence concerning the risk of PUD for patients who are taking glucocorticoid monotherapy. Two metaanalyses found no increased risk of PUD for patients who were taking glucocorticoids, while another found PUD to be a rare complication of corticosteroid therapy, occurring in <0.4% to 1.8% of patients.<sup>1-3</sup> In a nested case-control study of Medicaid patients, there was no increased risk of peptic ulcer disease at any dose or duration of glucocorticoid therapy.<sup>4</sup> Patients who are taking glucocorticoids may experience more symptoms of gastric irritation, yet in 2 separate studies these symptoms did not translate into an increased risk for PUD.<sup>1,5</sup> However, the combination of glucocorticoids with nonsteroidal antiinflammatory drugs clearly increases the risk for PUD. In the same case-control study cited above, there was a significantly increased risk of developing ulcers among patients taking this combination (relative risk, 4.4 [95% confidence interval [CI], 2-9.7]).<sup>4</sup>

### GI bleed

As with PUD, the concomitant use of glucocorticoids and nonsteroidal antiinflammatory drugs increases the risk of GI bleeding. In 1 study, patients who were taking low-dose aspirin plus high-dose corticosteroid therapy had a relative risk of 4.3 (95% CI, 2.10-9.34) for developing upper GI bleeding compared to those taking low-dose aspirin alone. Patients taking low-dose aspirin with low- or medium-dose corticosteroids, however, did not have increased risk.<sup>6</sup> It is not clear whether glucocorticoid use alone increases GI bleeding.<sup>6-9</sup> A metaanalysis of 71 controlled, randomized trials showed a low but independent risk of bleeding caused by steroids.<sup>2</sup> In the study cited above, patients who were taking high-dose glucocorticoids alone had a slight increased relative risk for developing GI bleed of 1.89 (95% CI, 1.05-3.38).<sup>6</sup> Finally, a metaanalysis comparing glucocorticoid use to placebo found an increased risk of bleeding or perforation limited to hospitalized patients only.<sup>8</sup>

### Pancreatitis

The data linking pancreatitis to glucocorticoid use are similarly mixed. One case-control study found a nearly threefold increased risk of acute pancreatitis among current users of betamethasone, and a slightly lower but still significant risk among those taking prednisolone.<sup>10</sup> The risk reached its highest level in the first 4 to 14 days after the betamethasone was dispensed and 15 to 30 days after prednisolone, with the risk gradually decreasing thereafter.<sup>10</sup> In a randomized, placebo-controlled trial of steroids for



**Fig 1.** Approach to proton pump inhibitor prophylaxis for peptic ulcer disease. *NSAID*, Nonsteroidal antiinflammatory drug; *PPI*, proton pump inhibitor; *PUD*, peptic ulcer disease.

optic neuritis that also evaluated corticosteroid side effects, there was only 1 case of acute pancreatitis among 457 patients.<sup>5</sup> A retrospective chart review of patients with systemic lupus determined that glucocorticoids were not the etiologic agent among those who developed pancreatitis.<sup>11</sup>

### Management and prevention

Patients who must take a combination of glucocorticoids and nonsteroidal antiinflammatory drugs should be prescribed prophylaxis with a proton pump inhibitor (PPI). In patients with other risk factors for PUD, including those with previous peptic ulcer disease, heavy smokers, heavy alcohol users, patients >65 years of age, and patients taking other medications that may increase the risk of PUD, such as bisphosphonates, clinicians may choose to prescribe PPIs. For those taking glucocorticoids alone, without other risk factors, routine use of a PPI is not recommended (Fig 1). Patients should be counseled on the signs and symptoms of upper GI bleed, PUD, and, in the first 2 to 4 weeks of therapy, pancreatitis. These include black or tarry, melanic stools, fatigue, pallor, and severe abdominal pain, particularly if the pain is postprandial and radiating to the back or associated with nausea and vomiting.

### PPIs

PPIs are an effective means of prophylaxis for PUD and GI bleeding. Esomeprazole 20 mg and 40 mg, pantoprazole 20 mg and 40 mg, lansoprazole 15 mg and 30 mg, omeprazole 20 mg and 40 mg, and rabeprazole 20 mg are all approved for prophylaxis. All are administered daily before breakfast, and, if needed, a second dose can be given before the evening meal. The choice of which PPI to prescribe comes down to cost, accessibility, and patient preference. However,

**Table I.** Laboratory definitions of diabetes\*

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Hemoglobin A1c $\geq 6.5\%$ <sup>†</sup>
Fasting plasma glucose $\geq 126$ mg/dL (7.0 mmol/L) <sup>‡</sup>
Fasting is defined as no caloric intake for $\geq 8$ hours
Two-hour plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) during an oral glucose tolerance test
Random plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia

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\*The first 3 criteria should be repeated if abnormal. Two abnormal tests indicate a diagnosis of diabetes.

<sup>†</sup>In patients with ongoing steroid treatment, hemoglobin A1c can be used to monitor blood sugars, but not before 3 months of steroid therapy.

<sup>‡</sup>Postprandial hyperglycemia is more common than fasting hyperglycemia with glucocorticoid use, and postprandial testing may therefore be a more sensitive indicator.

drug–drug interactions should also be considered. In recent years, studies have linked PPIs to certain adverse reactions, including an increased risk for enteric infections, such as *Clostridium difficile* colitis, decreased micronutrient absorption, rebound acid hypersecretion, increased fracture risk, chronic kidney disease, and dementia; however, the data are often conflicting.<sup>12-15</sup> The US Food and Drug Administration continues to advise against the combination of omeprazole and clopidogrel out of a concern that the resulting drug–drug interaction will decrease the antiplatelet efficacy of clopidogrel.<sup>16</sup> The data as to the clinical relevance of this interaction remain mixed.<sup>12</sup> However, it may be prudent to select a different PPI in this situation. As with any drug, a PPI should be prescribed only when clinically indicated and at the lowest effective dose. For the purpose of prophylaxis, this should be the recommended once daily starting dose for each specific agent. If the therapeutic response is inadequate, the dose can be increased or given twice daily. If PUD symptoms persist or signs of GI bleeding develop, referral to the patient's primary care provider or gastroenterologist is prudent.

## ENDOCRINE (DIABETES, ADRENAL SUPPRESSION, AND CUSHING SYNDROME)

### Key points

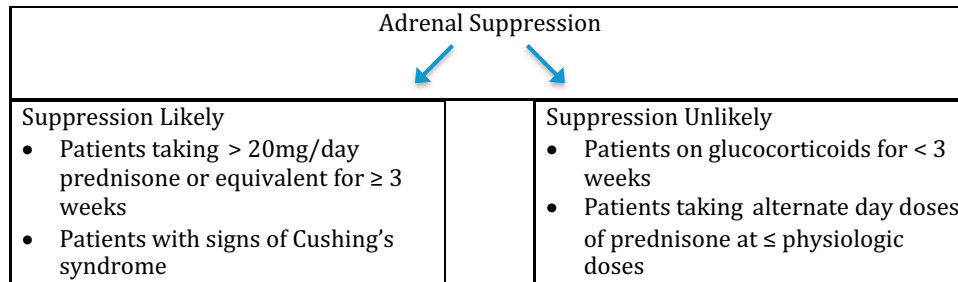
- **Glucocorticoid therapy can cause diabetes, adrenal suppression, and Cushing syndrome**
- **Adrenal suppression is not uncommon among patients who are taking glucocorticoids, and the management of this potentially devastating side effect requires careful consideration**

### Diabetes

Glucocorticoids can worsen existing diabetes and cause steroid-induced diabetes. Typical characteristics include an exaggerated postprandial hyperglycemia and insensitivity to exogenous insulin.<sup>17</sup> The

response is dose-dependent. A case-control study of Medicaid patients evaluated the relative risk of starting hypoglycemic therapy while taking glucocorticoids and found an odds ratio of 1.77 (95% CI, 1.54-2.02) for doses  $<10$  mg/day of prednisone equivalent versus 10.34 (95% CI, 3.16-33.90) for doses  $\geq 30$  mg/day.<sup>18</sup> With steroid use, postprandial hyperglycemia (defined as blood glucose  $>200$  mg/dL 2 hours after a meal) is more common than fasting hyperglycemia and is a much more sensitive indicator of steroid-induced diabetes.<sup>19</sup> In an observational study of patients receiving prednisolone for chronic obstructive pulmonary disease, the use of continuous blood glucose monitoring demonstrated hyperglycemia predominantly occurring in the afternoon and evening.<sup>20</sup> Risk factors for steroid-induced diabetes include older age and higher body mass index.<sup>19</sup> Alternate-day dosing is also associated with steroid-induced diabetes.<sup>21</sup>

**Monitoring.** All patients should be counseled regarding the risk of hyperglycemia and the signs and symptoms of diabetes, including polyuria, polydipsia, and polyphagia. Monitoring and treatment should be conducted in conjunction with the patient's primary care doctor or other treating physicians, such as an endocrinologist. Guidelines for when and how to initiate blood glucose monitoring in patients taking glucocorticoids are not clearly delineated in the literature. Consider checking a baseline glycated hemoglobin with presteroid laboratory values; patients with borderline or elevated glycated hemoglobin levels at baseline warrant additional evaluation and closer monitoring. Lifestyle modifications should be encouraged, but these may be insufficient for steroid-induced diabetes,<sup>22</sup> and the underlying disease process may limit exercise capacity. Routine monitoring of blood glucose levels via finger stick or basic metabolic panel should be included with regular medication monitoring or laboratory monitoring of the underlying disease state. In



**Fig 2.** Guidelines for assessing the risk of adrenal suppression.

addition, consider prescribing a glucometer to patients who are expected to be taking chronic glucocorticoid therapy, with instructions to check random blood sugar in the afternoons at least 2 to 3 times per week. Glucose readings >200 mg/dL should prompt a phone call to the clinician, more regular blood sugar monitoring, and referral to the patient's primary care doctor or endocrinologist. Laboratory definitions of diabetes are provided in [Table I](#).

**Treatment.** Clinicians should treat to the same glycemic targets in glucocorticoid-induced diabetes as in those with preexisting diabetes. A patient's primary care provider or endocrinologist should manage clinically relevant hyperglycemia. Patients who are taking insulin or sulfonylureas (which increase endogenous insulin production) who are tapering their glucocorticoid dose should be reminded to monitor their blood glucose level closely while tapering, because they are at risk for life-threatening hypoglycemia. The patient's other treating physicians should be kept abreast of such intended changes in the glucocorticoid regimen so that they can provide assistance with monitoring and adjusting these medications.

### Adrenal suppression/steroid taper

Glucocorticoid use suppresses the hypothalamic–pituitary–adrenal (HPA) axis. Too abrupt a withdrawal of glucocorticoids may result in symptoms of adrenal suppression, the steroid withdrawal syndrome, or a recurrence of the underlying condition for which glucocorticoids were prescribed. Symptoms of adrenal suppression include weakness, fatigue, nausea, vomiting, diarrhea, abdominal pain, fever, weight loss, myalgias, arthralgias, and malaise. Adrenal crisis manifests with hypotension, decreased consciousness, lethargy, seizures, coma, and hypoglycemia.

Studies estimate daily physiologic cortisol production at 5 to 7 mg/m<sup>2</sup>/day. Higher doses are considered supraphysiologic.<sup>23-26</sup> Patients should be considered adrenally suppressed if they are

taking doses of prednisone of ≥20 mg daily for ≥3 weeks.<sup>27</sup> Clinical signs of Cushing syndrome also suggest adrenal suppression. Patients who are taking glucocorticoids for <3 weeks and those treated on alternate days with doses less than or equal to physiologic levels are less likely to have adrenal suppression.<sup>27-29</sup> However, individual responses to glucocorticoids may be highly varied, and dose and duration of therapy may not adequately reflect HPA axis suppression.<sup>30</sup> For example, patients taking prednisone doses as low as 5 mg/day for a few weeks or 40 mg after even 1 day may show evidence of adrenal suppression, but this is not necessarily clinically relevant.<sup>30-32</sup> Appropriate caution is advised with any taper. Guidelines for assessing the risk of adrenal suppression are noted in [Fig 2](#).

**Tapering.** A systematic literature review found insufficient evidence to recommend any particular strategy for tapering glucocorticoids.<sup>33</sup> Tapering regimens vary with the underlying disease state and should be adjusted based on disease activity and medical comorbidities. Patients experiencing severe glucocorticoid-related side effects while achieving disease control may benefit from more rapid tapers. Patients with ongoing disease activity may require slower tapers. An example taper of long-term steroids for pemphigus vulgaris (assuming disease control) designed to minimize the risk of disease flare and adrenal insufficiency is shown in [Table II](#).<sup>34</sup> In general, below doses of 10 to 15 mg prednisone per day, tapering of chronic steroids should slow to 1 to 2.5 mg every 1 to 3 weeks to account for HPA axis suppression, as warranted by disease activity. In the absence of clear guidelines, clinical judgment and close observation are necessary. Tapers can be managed with or without monitoring morning plasma cortisol levels, and clinicians may choose to switch glucocorticoids to hydrocortisone once a physiologic dose is achieved before continuing to taper.

At any point during a taper, a patient may experience symptoms of adrenal insufficiency or steroid withdrawal syndrome. Steroid withdrawal syndrome

**Table II.** Long-term steroid taper for pemphigus vulgaris\*

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For patients taking >40 mg/day prednisone:  
Taper steroids by 10 mg/week to 40 mg prednisone daily  
Remain on 40 mg/day for 1 week  
Starting at 40 mg/day prednisone:  
Taper by 5 mg/week to a dose of 20 mg prednisone daily  
Stay on 20 mg prednisone daily for 1 week  
Starting at 20 mg/day prednisone  
Taper by 2.5 mg/week to a dose of 5 mg daily  
Stay on 5 mg prednisone daily for 1 week  
Starting at 5 mg/day prednisone  
Taper by 1 mg/week  
Continue taper until patient is off steroids

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\*Taper slowly to avoid disease flare and adrenal insufficiency. This taper may be used for other dermatoses requiring high-dose glucocorticoid therapy. However, clinicians must individualize any taper based on disease activity, disease, and underlying comorbidities. This example does not apply to all patients or all diseases but is presented for reference.

is marked by symptoms of adrenal insufficiency (such as weakness, fatigue, nausea, vomiting, etc) in patients with normal HPA axis testing.<sup>35</sup> Patients should be advised of these signs and symptoms and counseled to cease tapering and contact a physician immediately if they develop. The taper should be temporarily halted, and hydrocortisone or an increased dose of the glucocorticoid should be given until the patient stabilizes. The clinician may also choose to test the HPA axis at this time. Patients should resume tapering at a slower rate in 2 to 4 weeks. There are no specific guidelines about rechecking the HPA axis upon resumption of the taper or steroid cessation, but close monitoring and slow taper are advised. Consulting an endocrinologist is also advised for any patient who experiences adrenal insufficiency.

Serious illnesses and major surgeries may require stress dose steroids for patients who have taken glucocorticoids for  $\geq 1$  month.<sup>36,37</sup> Depending on the surgery or illness, various methods of glucocorticoid replacement therapy can be considered. This should be discussed with the patient's surgical or hospital team. Patients need not show symptoms of adrenal suppression before illness or surgery. It is important to ensure that the patient and other providers are aware that the patient is taking steroids and may require dose augmentation to avoid adrenal crisis. Patients who are taking long-term steroids should carry a glucocorticoid treatment card or wear a medic alert bracelet denoting their risk of life-threatening adrenal suppression.

### Cushing syndrome

Classic characteristics of Cushing syndrome include central obesity, redistribution of body fat to truncal areas, supraclavicular fat pads, striae distensae, proximal muscle weakness, fatigue, hypertension, acne, glucose intolerance, muscle atrophy, and psychologic disturbances.<sup>35</sup> Every mode of exogenous glucocorticoid use has been associated with Cushing syndrome. These effects are directly related to the dose and duration of use. Predicting the correct dose and time-course at which Cushing syndrome develops is complicated by the various potencies and half-lives of glucocorticoids; however, even doses as low as 5 mg/day of prednisone can result in Cushing syndrome.<sup>35</sup> In 1 study, the prevalence of Cushing syndrome increased linearly with increasing glucocorticoid dose, from 4.3% to 15.8% to 24.6% among patients taking <5 mg, 5 to 7.5 mg, and >7.5 mg of prednisone daily over the course of 6 months.<sup>38</sup> Medications that interfere with the cytochrome P450 system may prolong the half-life of glucocorticoids, increasing the risk of Cushing syndrome. Management includes reducing the dose and duration of glucocorticoid therapy, as able, to avoid and ameliorate this complication. Clinicians are advised to check drug–drug interactions before prescribing any medication concomitantly with glucocorticoids.

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