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

Ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients

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Learning objectives
After completing this learning activity, participants should be able to describe the ocular, cardiovascular, muscular, and psychiatric side effects of glucocorticoid use and devise strategies to prevent complications in adult and pediatric patients taking glucocorticoids.

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The final article in this 4-part continuing medical education series reviews the ocular, cardiovascular, muscular, and psychiatric side effects of glucocorticoids and discusses side effects unique to pediatric patients. (J Am Acad Dermatol 2017;76:201-7.)

Key words: cataracts; glucocorticoids; glaucoma; growth suppression; side effects; steroid myopathy; steroid psychosis; steroids.

OCULAR ADVERSE EVENTS

Key points

- **The risk for developing glaucoma and cataracts while taking glucocorticoid therapy appears to be dose-dependent**
- **When long-term glucocorticoid therapy is planned, clinicians should ask about the history of glaucoma and cataracts and consider referral for ophthalmologic examination**

Glucocorticoid use increases the risk of glaucoma and cataracts.[1] The risk appears to be both duration and dose-dependent. In 1 study, glaucoma risk increased with doses >7.5 mg of prednisone per day taken for ≥6 months.[2] A separate case-control study found an increased risk for glaucoma among patients who had taken glucocorticoids within 2 weeks, but not for those who had previously taken glucocorticoids.[1] The risk for glaucoma increased over time and for all doses of

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glucocorticoids; however, doses of hydrocortisone >40 mg per day (prednisone 10 mg equivalent) were associated with an almost 2-fold increased risk for glaucoma.[1]

Importantly, patients may not be aware of early visual loss. The increase in intraocular pressure is painless, but it can lead to permanent optic nerve damage. Discontinuation of glucocorticoid therapy leads to reversal of intraocular hypertension within 2 weeks, at which time pressures appear to normalize.[1]

Increased risk for posterior subcapsular cataracts can also be associated with long-term glucocorticoid use.[3] In 1 study, 39% of patients with rheumatoid arthritis developed cataracts, but only at prednisone doses of >10 mg per day for ≥1 year.[4] In a study of 230 patients with systemic lupus who were taking prednisone for 5 years, only 6 developed cataracts at doses ranging from 8 to 30 mg prednisone per day.[5] Another study of lupus patients found that cumulative prednisone dose was significantly associated with increased risk for cataracts at a reference dose of 10 mg per day for 10 years.[6] This side effect is more likely to occur at higher glucocorticoid doses, but as with other steroid-related complications, even doses ≤5 mg prednisone per day have been linked to cataract formation.[2] Therefore, there may be no safe dose at which clinicians can disregard this complication completely.[3,7] Other side effects, such as exophthalmos and chorioretinopathy, rarely occur.

Management. Clinicians should inquire about personal and family history of glaucoma or cataracts before starting glucocorticoid therapy. All patients for whom long-term glucocorticoid therapy at any dose is planned should have a baseline ophthalmology evaluation, with additional management and regular follow-up based on findings at the initial visit, the underlying disease, comorbidities, and anticipated steroid course (Table I). In the event an ophthalmologic examination cannot be performed in a timely fashion before beginning glucocorticoid therapy, patients can be referred after therapy has started. Given the risk of diabetic retinopathy with poor glucose control and the association of glucocorticoid use with diabetes, adequate diabetes management is also important to mitigate ocular complications of corticosteroids.

Table I. Ocular side effects

Ask about history of cataracts and glaucoma
Consider referral for baseline ophthalmology examination
Follow-up ophthalmologic examination as needed (check intraocular pressure after about 3 months of systemic steroids)

CARDIOVASCULAR/HYPERTENSION/LIPIDS

Key point

- **Glucocorticoid therapy may increase the risk of cardiovascular disease, as may the patient's underlying inflammatory condition**

Cardiovascular

Glucocorticoids may increase the risk of cardiovascular disease. One large case-control study found a dose-response relationship between daily glucocorticoid dose and the risk of heart failure among current users of glucocorticoids, including patients with rheumatoid arthritis, chronic obstructive pulmonary disease, and other conditions. The risk of ischemic heart disease was also increased, but there was not an association with cerebrovascular disease.[8] In a large, population-based study, patients taking ≥7.5 mg of prednisone per day or the equivalent had a significantly higher composite risk of myocardial infarction, angina, coronary revascularization, hospitalization for heart failure, transient ischemic attack, and stroke.[9] Patients taking glucocorticoids within the preceding 6 months were at increased risk. Continuous use (≤180 days between prescriptions) was also associated with higher risk compared to intermittent use.[9] Patients with iatrogenic Cushing syndrome have a higher hazard ratio of developing a cardiovascular event and a higher risk of coronary heart disease and cardiac insufficiency.[10]

The association between cardiovascular disease and glucocorticoid use is confounded by the underlying inflammatory condition, which may increase the incidence of cardiovascular disease because of chronic inflammation and the need for higher doses of glucocorticoids. For example, increased mortality from heart disease has been noted among patients with inflammatory arthritis; however, many patients have been treated with high-dose steroids.[9]

Pulse glucocorticoids, defined as high-dose glucocorticoids delivered over a short period of time, are used to treat severe inflammatory disorders and are also associated with cardiovascular disease. Sudden death caused by pulse dose glucocorticoids has been reported, usually if given over <2 hours, but this tends to occur in patients with underlying cardiac disease or in patients receiving steroids for nondermatologic conditions.[11] Continuous cardiac monitoring should be considered in patients with severe cardiac or kidney disease who are receiving pulse dose glucocorticoids.[11] Patients treated for

dermatologic conditions with widespread cutaneous erosions may benefit from continuous monitoring during pulse therapy because of the potential for electrolyte shifts resulting from loss of skin integrity.[11]

Hypertension and hyperlipidemia

The mechanism behind glucocorticoid-induced hypertension remains unclear. Increasing evidence supports the notion that activation of mineralocorticoid receptors may not be the primary mechanism. Vascular tone and possibly centrally mediated mechanisms may also play a role.[12]

Glucocorticoid use may result in hyperlipidemia, but the literature is inconsistent.[13] After renal and cardiac transplantation, tapering of steroids mirrors a decrease in cholesterol level.[14] For patients with inflammatory disorders, however, some studies suggest an improved atherogenic profile in corticosteroid-treated patients paralleling decreased disease activity.

Management. Cardiovascular risk factors should be aggressively managed in all patients who are taking glucocorticoids. All should receive lifestyle counseling; hypertension and hyperlipidemia should be treated according to current guidelines. Antihypertensive drugs that target vascular resistance may be beneficial.[15] Thiazide diuretics may ameliorate hypertension and may also lower osteoporosis risk by decreasing calcium excretion. However, thiazide diuretics can also cause hyperglycemia, among other side effects. There are no current guidelines for lipid monitoring in patients taking glucocorticoids. Evidence-based recommendations support baseline lipid screening; recommendations for repeat evaluation are less well established outside of transplant recipients. Frequency will vary based on the initial lipid profile, comorbidities, underlying disease state, dose, and duration of glucocorticoid exposure. In the absence of established guidelines, we suggest checking biannual lipid profiles in patients taking glucocorticoids chronically unless there is an indication for more frequent monitoring. Lipid-lowering medications should be prescribed in conjunction with a patient's primary care doctor.

MYOPATHY

Key points

- **The diagnosis of steroid myopathy is a clinical diagnosis based on characteristic symptoms without a more likely alternative diagnosis**
- **Higher doses of steroids for longer periods of time increase the risk**
- **Clinicians may need to taper glucocorticoid therapy to diagnose steroid myopathy definitively**

Presentation

Glucocorticoid-induced myopathy presents with painless muscle weakness, followed by atrophy, starting in the proximal lower extremities and spreading to the proximal upper extremities and distal sites.[16] Patients may complain of progressive difficulty standing from a seated position, climbing stairs, and performing overhead activities.[17]

Mechanism

A wide body of literature exists on the mechanism of glucocorticoid-induced myopathy. In brief, the effect of glucocorticoids on muscle is thought to be both catabolic and antianabolic, causing atrophy of type II muscle fibers through muscle proteolysis and decreased muscle protein synthesis.[18]

Risk factors

The risk of developing steroid myopathy appears to increase with greater steroid dose and duration,[19,20] but wide variation is reported. In 1 study, prednisone doses of >40 mg per day significantly increased the risk.[21] Fluorinated synthetic steroids, such as dexamethasone, are associated with a greater risk of steroid myopathy than nonfluorinated steroids, such as prednisone and prednisolone.[17] The risk of steroid myopathy may be minimized with alternate day dosing.[21]

Workup

The diagnosis of steroid myopathy is a clinical diagnosis. Creatinine kinase levels are normal, which helps distinguish steroid myopathy from underlying inflammatory muscle disease. Electromyography is typically unremarkable, with only mild changes in some individuals.[17] Serum markers, such as lactate dehydrogenase and aspartate aminotransferase, are also normal. The clinical utility of creatinuria, suggested in some studies as a marker for steroid myopathy, has been called into question.[21,22] Therefore, one must have a high index of suspicion for steroid myopathy in patients who experience weakness after the onset of glucocorticoid therapy or an increase in glucocorticoid dose. This possibility can be a source of confusion in patients receiving glucocorticoids for dermatomyositis and those taking steroids along with hydroxychloroquine, which can also cause myopathy.

Management. When steroid myopathy is suspected, glucocorticoids should be tapered safely, monitoring for a flare of the underlying inflammatory

condition and remaining vigilant for signs of adrenal insufficiency. Improved strength within 3 to 4 weeks helps establish the diagnosis of glucocorticoid myopathy.[16] Various medications, including creatine, androgens, potassium, and vitamins have been investigated for use in steroid myopathy; however, more research is needed before they can be recommended.[17,18] Clinicians may consider switching to nonfluorinated steroids, such as prednisolone or hydrocortisone. Referral to a physical therapist may be warranted.

MOOD AND COGNITIVE EFFECTS

Key points

- **Glucocorticoids are associated with a range of psychiatric side effects that appear to be dose-dependent**
- **Clinicians should ask about a history of psychiatric disorders and comanage patients with a psychiatrist when appropriate**

General psychiatric symptoms

Glucocorticoids are associated with mood disorders, anxiety, depression, panic disorder, psychosis, delirium, confusion, and suicide, and they can produce cognitive deficits, especially related to memory.[23,24] These side effects appear to be dose-dependent. Reports suggest that the majority of patients taking moderate- to high-dose glucocorticoids (>10 mg/day, but more often >20 mg/day) will experience some degree of behavioral symptoms.[25] Short-term therapy, as for asthma exacerbation, may lead to hypomania. Euphoria or psychosis is more common with high doses. Depressive symptoms can occur with long-term therapy.[25,26] Previous neuropsychiatric disorders and larger daily doses of glucocorticoids are associated with a greater risk of these side effects.[24]

Steroid psychosis

Steroid psychosis is a more serious complication that is marked by a range of symptoms, including psychosis, dementia, delirium, depression, and suicidality.[27] Doses <40 mg per day are unlikely to provoke severe psychiatric illness; however, doses >80 mg per day are significantly associated with these effects.[28] Onset of symptoms may occur within a few days to a few weeks of initiating therapy.[27] Symptoms may also arise during glucocorticoid taper.[29]

Age and sex

In a large epidemiologic study involving >300,000 primary care patients exposed to glucocorticoids, age and sex were risk factors for specific behavioral side effects. Women were more likely to develop depression, whereas men were more likely to develop mania.[24] The risk of depression, mania, delirium, confusion, and disorientation increases with age, but the opposite is true of suicidal behavior and panic disorder.[24] The incidence of neuropsychiatric events is highest in the first 3 months of therapy.

Table II. Mood and cognitive effects

General recommendations before initiating glucocorticoid therapy
Ask about history of neuropsychiatric disease, paying special attention to any tendency toward self-harm
Consider ongoing mental health screening while taking glucocorticoids
Advise family members to contact clinicians with concern of any change in behavior
Insomnia
Dose glucocorticoids in the morning only, taper dose if possible
Consider low-dose sleep aid, depending on clinical situation
Depression/steroid mania/suicidality
Comanage patient with psychiatrist or primary care physician
Attempt glucocorticoid dose reduction, if possible
Monitor patients closely; urgent inpatient admission for suicidality or severe symptoms

Management. Patients and their friends and family members should be cautioned about the potential for mood swings, insomnia, emotional lability, rapid speech, increased energy, and related symptoms (Table II). All patients, especially younger ones, should be asked about any history of neuropsychiatric disorders or suicidality before glucocorticoid initiation and during therapy. Clinicians should clearly ask about a history of self-harm and any thoughts or plans for self-harm. Those with histories as noted should be referred to primary care physicians or psychiatrists. Hospital admission should be considered if concern for suicidal thoughts or plans arises.

When patients experience psychiatric side effects, they should be referred promptly to a primary care provider or psychiatrist. Psychiatric symptoms may interfere with treatment of the underlying condition. Those experiencing sleep impairment should take glucocorticoids early in the day rather than in the evening. Dose reduction or tapering and discontinuation of steroids is advised if significant symptoms occur. When that cannot be accomplished because of the underlying condition, anxiolytics and

antidepressants may be prescribed. Expert assistance from mental health professionals is advised for patients who develop psychiatric side effects of glucocorticoid therapy, especially when complications are severe or glucocorticoid regimens cannot be tapered.

SPECIAL CONSIDERATIONS IN THE PEDIATRIC PATIENT

Key points

- **There is significant overlap in the glucocorticoid complications seen in adult and pediatric populations**
- **Certain complications, such as cataracts, bone health, and growth suppression, impact the pediatric population more uniquely**

Cataracts

Children taking glucocorticoids may be more susceptible to developing cataracts compared to adults.[30] As such, they may require additional ophthalmologic screening. Physicians should take a careful family history of eye disease when initiating glucocorticoids in pediatric patients and refer them for baseline ophthalmologic examination. Children who experience delayed bone age and growth suppression from steroids are at increased risk of developing cataracts.[30]

Growth suppression

Glucocorticoid therapy has repeatedly been shown to result in growth suppression among pediatric populations.[31-36] There are multiple mechanisms underlying this complication. Glucocorticoids inhibit bone formation, increase calcium excretion, promote bone resorption, and interfere with nitrogen and mineral balance.[35] In addition, glucocorticoids interfere with growth hormone secretion, growth hormone receptor expression, and growth hormone effect on target tissue.[35] Aside from growth suppression, pediatric bone health may be impacted by osteopenia, which can occur in children on glucocorticoids because of high bone turnover.[37]

Growth suppression is correlated with daily dose, duration, route of administration, and type of glucocorticoid prescribed.[33,35] Glucocorticoid exposure is highly correlated with reduction in growth velocity. Glucocorticoids with high systemic exposure, such as oral prednisolone, cause greater growth suppression than those without significant systemic exposure, such as intranasal fluticasone proprionate.[34] The type of glucocorticoid also influences growth suppression because of differences in half-life.[35,36] For example, prednisone, which has a longer half-life than hydrocortisone, carries a greater risk of growth suppression.[35] Glucocorticoids dosed at physiologic levels (according to some authors, hydrocortisone 12-15 mg/m^2/day and others hydrocortisone as low as 6 mg/m^2/day) and alternate-day therapy have been implicated in growth suppression, although the risk appears to be lower.[31,33,35,38] Children who experience growth suppression from glucocorticoid use may not catch up in height even after glucocorticoids are stopped.[33,35,36] Physicians must therefore attempt to wean glucocorticoids as soon as possible in pediatric patients and refer patients to a primary care provider for routine height measurement. Referral to a pediatric endocrinologist for assistance with management is highly recommended for any patient who requires ongoing or repeated doses of glucocorticoids for disease management.

Diabetes

Physicians must also pay close attention to hyperglycemia and diabetes in pediatric patients who are taking glucocorticoids. These patients can develop medication-induced diabetes without having the same risk factors as children who develop type 2 diabetes. A retrospective study of risk factors for medication-induced diabetes among pediatric patients found that traditional risk factors, such as family history, race, obesity, and acanthosis nigricans, were less often present in medication-induced diabetes than in children with type 2 diabetes.[39] Physicians prescribing glucocorticoids to pediatric populations may therefore need to have a lower threshold to begin testing for and treating this complication.

Adrenal suppression

Pediatric patients are also at risk for adrenal suppression. As in adults, the dose and duration of glucocorticoid therapy correlate with risk. A review of 59 pediatric patients with inflammatory bowel disease who were taking prednisolone at a median dose of 5 mg daily for 4.7 months found that 20% had adrenal suppression; the rate was higher in patients treated with higher doses and for longer duration.[40] A recent Cochrane review of the hypothalamic-pituitary axis function after glucocorticoid therapy for childhood acute lymphoblastic leukemia found that adrenal insufficiency commonly occurred after cessation of glucocorticoid therapy.[41] It is recommended that children on supraphysiologic doses of glucocorticoids for >2 weeks be considered at increased risk of adrenal suppression.[42] These patients should be weaned to doses that are less

than physiologic as soon as the underlying condition allows, or they can be considered for every other day dosing of glucocorticoids. Repeated short (<7-day) courses of oral steroids may also result in evidence of adrenal suppression by adrenocorticotropic testing, but it is unclear if this is clinically relevant.[43-45]

In conclusion, side effects of glucocorticoid therapy are a significant source of morbidity and mortality. Managing these side effects requires concerted counseling, prophylaxis, and medication management. The evidence summarized here and in the accompanying tables is provided to help clinicians avoid and ameliorate these complications. Table I in the first article in this series is provided as a quick reference to the main points of discussion. Patients require careful instruction in order to anticipate these effects and alert clinicians to symptoms that may be vague and nonspecific. In this way, clinicians and patients can work together to limit the unintended harmful effects of glucocorticoids while seeking to maximize their therapeutic potential.

REFERENCES

1. Garbe E, Lelorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet*. 1997;350:979-982.
2. Huscher D, Thiele K, Gromnica-ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis*. 2009;68:1119-1124.
3. Urban RC, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol*. 1986;31:102-110.
4. Black RL, Oglesby RB, Von Sallmann L, Bunim JJ. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. *JAMA*. 1960;174:166-171.
5. Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2014;53:1470-1476.
6. Zonana-nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum*. 2000;43(8):1801-1808.
7. Skalka HW, Prchal JT. Effect of corticosteroids on cataract formation. *Arch Ophthalmol*. 1980;98(10):1773-1777.
8. Souverein PC, Berard A, Van staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart*. 2004;90(8):859-865.
9. Wei L, Macdonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764-770.
10. Fardet L, Petersen I, Nazareth I. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. *BMJ*. 2012;345:e4928.
11. White KP, Driscoll MS, Rothe MJ, Grant-kels JM. Severe adverse cardiovascular effects of pulse steroid therapy: is continuous cardiac monitoring necessary? *J Am Acad Dermatol*. 1994;30(5 Pt 1):768-773.
12. Baum M, Moe OW. Glucocorticoid-mediated hypertension: does the vascular smooth muscle hold all the answers? *J Am Soc Nephrol*. 2008;19:1251-1253.
13. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 part B):2889-2934.
14. Pirsch JD, D'Alessandro AM, Sollinger HW, et al. Hyperlipidemia and transplantation: etiologic factors and therapy. *J Am Soc Nephrol*. 1992;2(12 suppl):S238-S242.
15. Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. *Pediatr Nephrol*. 2012;27:1059-1066.
16. Pereira RM, Freire de Carvalho J. Glucocorticoid-induced myopathy. *Joint Bone Spine*. 2011;78:41-44.
17. Minetto MA, Lanfranco F, Motta G, Allasia S, Arvat E, D'Antona G. Steroid myopathy: some unresolved issues. *J Endocrinol Invest*. 2011;34:370-375.
18. Schakman O, Gilson H, Thissen JP. Mechanisms of glucocorticoid-induced myopathy. *J Endocrinol*. 2008;197:1-10.
19. Vecht CJ, Hovestadt A, Verbiest HB, Van Vliet JJ, Van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. *Neurology*. 1994;44:675-680.
20. Batchelor TT, Taylor LP, Thaler HT, Posner JB, Deangelis LM. Steroid myopathy in cancer patients. *Neurology*. 1997;48:1234-1238.
21. Bowyer SL, Lamothe MP, Hollister JR. Steroid myopathy: incidence and detection in a population with asthma. *J Allergy Clin Immunol*. 1985;76(2 part 1):234-242.
22. Shimohata T, Umeda M, Tanaka K, Nishizawa M. Reevaluation of validity of percent creatinuria for diagnosing steroid myopathy [in Japanese]. *No To Shinkei*. 2006;58:39-42.
23. Kenna HA, Poon AW, De Los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci*. 2011;65:549-560.
24. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am J Psychiatry*. 2012;169:491-497.
25. Wolkowitz OM, Burke H, Epel ES, Reus VI. Glucocorticoids. Mood, memory, and mechanisms. *Ann N Y Acad Sci*. 2009;1179:19-40.
26. Brown ES, Chandler PA. Mood and cognitive changes during systemic corticosteroid therapy. *Prim Care Companion J Clin Psychiatry*. 2001;3:17-21.
27. Hall RC, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. *J Nerv Ment Dis*. 1979;167:229-236.
28. Acute adverse reactions to prednisone in relation to dosage. *Clin Pharmacol Ther*. 1972;13:694-698.
29. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. *Ann N Y Acad Sci*. 2009;1179:41-55.
30. Covar RA, Leung DY, McCormick D, Steelman J, Zeitler P, Spahn JD. Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. *J Allergy Clin Immunol*. 2000;106:651-659.
31. Allen DB. Growth suppression by glucocorticoid therapy. *Endocrinol Metab Clin North Am*. 1996;25:699-717.
32. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol*. 1994;93:967-976.
33. Reimer LG, Morris HG, Ellis EF. Growth of asthmatic children during treatment with alternate-day steriods. *J Allergy Clin Immunol*. 1975;55:224-231.
34. Daley-Yates PT, Richards DH. Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a pharmacokinetic/pharmacodynamic model. *Clin Ther*. 2004;26:1905-1919.

35. Allen DB. Influence of inhaled corticosteroids on growth: a pediatric endocrinologist's perspective. *Acta Paediatr*. 1998;87:123-129.
36. Lai HC, Fitzsimmons SC, Allen DB, et al. Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med*. 2000;342:851-859.
37. Brinn M, Hillenbrand K. Long-term corticosteroid use. *Pediatr Rev*. 2009;30:497-498.
38. Allen DB, Julius JR, Breen TJ, Attie KM. Treatment of glucocorticoid-induced growth suppression with growth hormone. National Cooperative Growth Study. *J Clin Endocrinol Metab*. 1998;83:2824-2829.
39. Amed S, Dean H, Sellers EA, et al. Risk factors for medication-induced diabetes and type 2 diabetes. *J Pediatr*. 2011;159:291-296.
40. Sidoroff M, Kolho KL. Screening for adrenal suppression in children with inflammatory bowel disease discontinuing glucocorticoid therapy. *BMC Gastroenterol*. 2014;14:51.
41. Gordijn MS, Gemke RJ, Van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. *Cochrane Database Syst Rev*. 2012;(5):CD008727.
42. Shulman DI, Palmert MR, Kemp SF. Adrenal insufficiency: still a cause of morbidity and death in childhood. *Pediatrics*. 2007;119:e484-e494.
43. Rieder MJ. The child with multiple short courses of steroid therapy. *Paediatr Child Health*. 2003;8:226.
44. Ducharme FM, Chabot G, Polychronakos C, Glorieux F, Mazer B. Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. *Pediatrics*. 2003;111:376-383.
45. Dolan LM, Kesarwala HH, Holroyde JC, Fischer TJ. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol*. 1987;80:81-87.

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