Bridging Gaps Amidst Limited Evidence for Glucocorticoid-Induced Adrenal Insufficiency

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Glucocorticoids (GCs) are highly effective in treating autoimmune and inflammatory disorders. The prevalence of oral GC use is estimated to be around 1% in adult populations in the United Kingdom [1,2] and United States [3]. In Korea, prescriptions of adrenal hormones, including GCs, significantly increased by 26.1% from 519,963,000 in 2013 to 655,788,000 in 2022 [4]. Despite their efficacy, even low-dose GCs can increase risks of cardiovascular disease [5], severe infections [6], hypertension [7], diabetes [8], osteoporosis and fractures [9,10], and overall mortality [11]. Chronic GC therapy suppresses the hypothalamic-pituitary-adrenal (HPA) axis, and the recovery of adrenal function varies greatly among individuals. GC-induced adrenal insufficiency (GIAI) requires careful education and management, and in rare cases of adrenal crisis, prompt diagnosis and treatment are crucial [12].

Considering the widespread use of GCs and the risk for GIAI, the recently published European Society of Endocrinology and Endocrine Society joint clinical practice guideline provides guidance on GIAI to assist clinicians caring for patients on chronic GC therapy [13].

General recommendations for GC therapy of non-endocrine conditions and patient education
The guideline recommends (i.e., strongly recommends) that patients who are either on or tapering off GCs for non-endocrine conditions generally do not require evaluation by an endocrinology specialist. This approach empowers non-endocrine specialists to manage GC therapy, optimizing healthcare resource utilization while ensuring patient safety. Clinicians are encouraged to educate patients about the endocrine aspects of GC therapy, including potential risks such as adrenal insufficiency (AI), and the importance of stress dosing during illness or surgery. Providing patients with access to current information about GC therapy enables them to manage their conditions effectively and reduces the risk of complications.

Recommendations for tapering systemic GC therapy, diagnosing GIAI, and managing GC withdrawal syndrome
In patients receiving short-term GC therapy (<3 to 4 weeks), irrespective of the dose, the guideline suggests (i.e., weakly recommends) discontinuing GCs without tapering or testing, due to a low risk of HPA axis suppression. For long-term GC therapy (3 to 4 weeks or more), tapering should be considered only when the underlying disease is controlled and GCs are no longer necessary. The tapering process should be continued until a physiologic daily dose equivalent is reached (Table 1).

The guideline recommends considering GC withdrawal syndrome during tapering. GC withdrawal syndrome arises when the GC dosage is reduced within the supraphysiologic range, leading to symptoms unrelated to the original disease or un-
treated AI. In cases of severe GC withdrawal syndrome, the GC dosage may be temporarily raised to the most recently tolerated level, and tapering may be prolonged. Routine testing for AI is not recommended for patients receiving supraphysiologic doses or for those who still require GC treatment for their underlying condition.

The guideline suggests that patients using long-acting GCs switch to shorter-acting alternatives when long-acting GCs are no longer necessary (Table 1). It also suggests that patients receiving a physiologic daily dose equivalent who wish to discontinue GC therapy should either gradually taper the dose while monitoring for clinical signs of AI or undergo morning serum cortisol testing (Fig. 1). The guideline recommends morning serum cortisol as the initial test to confirm HPA axis recovery, noting that higher values suggest an adequate adrenal response. Additionally, the guideline suggests against routinely conducting dynamic tests to diagnose AI in patients who are tapering or discontinuing GC therapy.

GIAI should be considered patients with current or recent use of non-oral GC formulations who present with signs and symptoms indicative of AI and those using multiple GC formulations simultaneously, high-dose inhaled GC or topical GC, or inhaled or topical GCs for >1 year, as well as those who have received intra-articular GC injections in the past 2 months or are receiving concomitant treatment with strong cytochrome P450 3A4 inhibitors. Patients with current or previous GC treatment who show signs and symptoms of exogenous Cushing syndrome are suggested to have GIAI. The guideline suggests that patients intending to discontinue GCs who do not show recovery of HPA

<table>
<thead>
<tr>
<th>Current daily PD equivalent dose</th>
<th>Suggested PD decrements</th>
<th>Time interval</th>
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</thead>
<tbody>
<tr>
<td>&gt;40 mg</td>
<td>5–10 mg decrease</td>
<td>Every week</td>
</tr>
<tr>
<td>20–40 mg</td>
<td>5 mg decrease</td>
<td>Every week</td>
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<tr>
<td>10–20 mg</td>
<td>2.5 mg decrease</td>
<td>Every 1–4 weeks</td>
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<tr>
<td>5–10 mg</td>
<td>1 mg decrease</td>
<td>Every 1–4 weeks</td>
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<tr>
<td>5 mg</td>
<td>In the absence of clinical symptoms or negative testing for AI, continue 1 mg decrease</td>
<td>Every 4 weeks</td>
</tr>
</tbody>
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PD, prednisone; AI, adrenal insufficiency.

*The approximate equivalent dose of PD 5 mg is hydrocortisone 20 mg, cortisone 25 mg, deflazacort 7.5 mg, prednisolone 5 mg, triamcinolone 4 mg, methylprednisolone 4 mg, dexamethasone 0.5 mg, and betamethasone 0.5 mg; *Low dosage PD preparations (e.g., 1 mg) are not available; the alternative is hydrocortisone with a 5-mg decrease.

Fig. 1. Two proposed approaches to systemic glucocorticoid (GC) discontinuation. HCS, hydrocortisone; PD, prednisone; PDL, prednisolone; MPD, methylprednisolone; DXM, dexamethasone; AI, adrenal insufficiency; NA, not applicable; CBG, cortisol binding globulin. ‘Exogenous GC should not be reduced below the lower end of the physiologic replacement dose range to ensure adequate replacement for AI, yet still providing a stimulus for hypothalamic-pituitary-adrenal (HPA) axis recovery. Further significant dose reduction should only occur with indication of HPA axis recovery; ‘Some patients with cortisol values close to the proposed 10.0 μg/dL (300 nmol/L) cutoff may still have a degree of suboptimal cortisol response when exposed to major stress. Rely on clinical judgement and offer stress GC coverage if AI is suspected in such cases. Dynamic testing may be considered; ‘Some patients may develop GC withdrawal symptoms (e.g., those who have been on supraphysiologic doses for a very long time) and may benefit from gradual tapering rather than an abrupt discontinuation.
axis function within 1 year while on a physiologic daily dose should be assessed for underlying causes of AI other than GIAI. It also suggests that patients on GCs with a history of adrenal crisis should be evaluated by an endocrinology specialist. Fludrocortisone is not recommended in patients with GIAI.

Recommendations for the diagnosis and therapy of adrenal crisis
The guideline recommends that patients who are currently using GCs or have used them recently and have not undergone biochemical testing to rule out GIAI should receive stress dose coverage during periods of stress exposure. The guideline presents general considerations for managing patients at risk of or diagnosed with GIAI during stress exposure, as well as examples of stress and suggested regimens.

The guideline suggests considering adrenal crisis as a diagnosis in patients who are currently using or have recently used GCs and have not undergone biochemical testing to exclude GIAI if they present with hemodynamic instability, vomiting, or diarrhea, regardless of the GC type, administration mode, or dose. Patients suspected of having an adrenal crisis should receive treatment with parenteral GCs and fluid resuscitation. The guideline also provides a detailed description of the signs and symptoms of adrenal crisis, potential precipitating factors, and the management of patients at risk of or diagnosed with GIAI who are suspected of experiencing an adrenal crisis.

Limitations and future research directions
Most of these recommendations have low or very low levels of evidence. Further research is needed to determine the true risk of clinical adrenal crisis and AI, identify the morbidity and mortality associated with GIAI, and establish risk factors for AI. It will be necessary to improve our understanding of GC withdrawal, develop specific and predictive tests and follow-up parameters to identify at-risk patients, identify better GCs with less impact on HPA axis suppression and an improved adverse effect profile, and harmonize cortisol assays using mass spectrometry.

Conclusion
In conclusion, this joint clinical guideline is a comprehensive resource for clinicians managing patients on long-term GC therapy. It provides guidance on tapering, monitoring, and managing GIAI, while emphasizing patient education and safety.

CONFLICTS OF INTEREST
No potential conflict of interest relevant to this article was reported.

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