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Original Research

Diagnostic performance of morning serum cortisol for glucocorticoid weaning in children and adults

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Abstract

Design: Morning cortisol predicts the outcome of the short synacthen test (SST). There is a paucity of studies examining this in a dedicated cohort of children and adults weaning off glucocorticoids and using a modern immunoassay. This study aimed to identify early morning serum cortisol (EMC) cut-offs which predict the SST outcome in children and adults during glucocorticoid weaning.

Methods: A retrospective cohort study of pediatric and adult patients on long-term glucocorticoids with suspected glucocorticoid-induced adrenal insufficiency (GIAI) undergoing an SST. Our main outcomes were cut offs with 95% and 99% sensitivity and specificity for EMC analysed on modern immunoassays, determined via receiver operating characteristic (ROC) curve analysis. A pass on SST was defined as 30-min cortisol of ≥430 nmol/L (15.6 µg/dL).

Results: 151 and 372 SSTs were included in the pediatric and adult cohorts, respectively, of which 32% and 37% were passed. ROC curve analysis demonstrated that EMC performed well in both cohorts with area under curve (AUC) of 0.79 (95% CI, 0.71, 0.87) and 0.88 (95% CI, 0.84, 0.91), respectively. EMC cut offs to predict a pass on SST were 278 (10.1 µg/dL) and 290 nmol/L (10.5 µg/dL) at 95% sensitivity, and 316 (11.5 µg/dL) and 349 nmol/L (12.7 µg/dL) at 99% sensitivity, respectively. Further analysis in adults showed that using a 95% cut off in clinical practice was effective as 48/51 patients with EMC between 290 and 349 nmol/L (10.5-12.7 µg/dL), were weaned off without adverse events.

Conclusion: Morning serum cortisol can predict the SST outcome in children and adults weaning from glucocorticoids. An EMC > 290 nmol/L in adults predicts a patient can stop glucocorticoid therapy and will recover adrenal function.

Keywords: morning cortisol, adrenal insufficiency, glucocorticoids, weaning, adult, pediatric

Significance

Up to 3% of the general population is taking systemic glucocorticoids at any given time and approximately half are at risk of developing Glucocorticoid-Induced Adrenal Insufficiency (GIAI). Joint European Society of Endocrinology/Endocrine Society guidelines and National Institute for Health and Care Excellence in the United Kingdom recommend early morning cortisol (EMC) thresholds to decide which patients can be weaned off glucocorticoids, but evidence has been lacking. This is the first study to derive EMC cut offs for both children and adults weaning from glucocorticoids using 2 different modern immunoassays. Our cut offs provide further evidence in support of the guidelines. We recommend that these cut-offs should be harmonized with clinical practice to reduce the need for dynamic testing.

Introduction

Glucocorticoids are commonly used in a wide array of inflammatory conditions and cancers.[1] Up to 3% of the general population can be on systemic glucocorticoids at any given time,[2] but this prevalence can be higher in some countries.[3] Glucocorticoid-Induced Adrenal Insufficiency (GIAI) results from the suppression of hypothalamic-pituitary-adrenal (HPA) axis due to adrenal gland atrophy caused by using long-term and/or high-dose glucocorticoids. Approximately half of all patients on oral glucocorticoids are at risk of GIAI and this risk increases with longer duration and higher cumulative dosages.[1,4]

Those on supraphysiological doses of glucocorticoids (≥5 mg of prednisolone or equivalent for 4 weeks or longer for adults and potentially lower doses taken for 3 weeks or longer for children) are at risk of developing GIAI and therefore need to be assessed before glucocorticoids are stopped.[5,6] Once glucocorticoids are weaned down to a physiological replacement dose, this assessment can be done clinically, seeking symptoms or signs of adrenal insufficiency, or through formal

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biochemical testing to assess the HPA axis.[6,7] The short synacthen test (SST), a dynamic test of adrenal function involving the injection of an analogue of ACTH (1,24-ACTH), is the most commonly used test of HPA axis function,[8–10]requiring patients to attend hospital/clinic for a minimum of 1-2 h and specialist staff to carry out the procedure. Although relatively safe, it is associated with complications including hypersensitivity allergic reactions,[11] and should only be performed in centers with immediate resuscitation facilities.[12] In recent years there have been shortages of synacthen, associated with large price increases and there are many parts of the world where it is unavailable.

Measurement of early morning cortisol (EMC) aims to capture the physiological circadian peak in cortisol and can help guide physicians in safely weaning patients off glucocorticoids. EMC testing can reduce the need for SSTs[13] and the joint European Society of Endocrinology (ESE) and Endocrine Society (ES) clinical guidelines on GIAI advise against the routine use of SST and recommend EMC as the first line test to confirm HPA axis recovery.[6] The National Institute for Health and Care Excellence (NICE) in the United Kingdom have recommended EMC cut-offs in adults and children[7] but there is a paucity of data with which to define these cut-offs. Larger studies are needed to assess the use of EMC, measured using contemporary immunoassays, in both pediatric and adult patients weaning from glucocorticoids.

At the time of diagnosis, adrenocorticotrophin hormone (ACTH) may be measured at baseline during an SST[14,15] to differentiate the underlying cause of AI (primary vs secondary/tertiary). The ability of ACTH or the cortisol:ACTH ratio to help predict the SST outcome in those on glucocorticoids is uncertain.

The aim of this study was to identify morning cortisol, ACTH, and cortisol:ACTH ratio cut-offs, measured using modern immunoassays, which predict the SST outcome in separate pediatric and adult cohorts weaning from glucocorticoids.

Methods

This was a retrospective observational cohort study of pediatric and adult patients who underwent an SST for suspected GIAI. The pediatric cohort was patients under 18 years of age on long-term glucocorticoids who underwent an SST between January 2019 and January 2024 at Sheffield Children's NHS Foundation Trust, UK. The patients in the adult cohort were all attending a dedicated endocrine steroid clinic and underwent an SST for suspected GIAI between September 2015 and April 2022 at Sheffield Teaching Hospitals NHS Foundation Trust UK. Patients on long-term oral [≥5 mg of prednisolone (or equivalent) for ≥4 weeks] or inhaled glucocorticoids, who underwent an SST for suspected GIAI were identified using electronic databases and any patient who had had an SST for any other indication were excluded. Electronic case notes of the patients on concurrent opioids were reviewed and cases where adrenal insufficiency was suspected due to GIAI were included. The baseline (0 minute) cortisol on SST was used as EMC. Patients were asked to attend the Endocrine Unit between 8 AM and 10:30 AM. Patients with known protein losing disorders, severe liver disease, on estrogens or pregnant were not included because of effects on cortisol-binding globulin and consequent total serum cortisol levels. SSTs performed on patients with active infections or adults on night shift work within the previous week were also excluded from the analysis as normal circadian rhythm is disrupted in these patients.

As per the established steroid weaning clinical care pathways in both hospitals, patients were first weaned down to a physiological replacement dose by the relevant specialty (in children ~6-8 mg/m^2/day hydrocortisone or prednisolone equivalent and in adults, prednisolone 3-5 mg/day or hydrocortisone 15-25 mg/day) and then a morning cortisol was performed. If the morning cortisol result was <336 nmol/L (12.2 µg/dL) in the pediatric cohort or <350 nmol/L (<12.7 µg/dL) in the adult cohort, the patient was referred to endocrinology for an SST, while maintaining them on a physiological steroid replacement dose. For pediatric patients who passed their SST we advised they stop their glucocorticoids with no further weaning or sick day/emergency cover but asked that they reported any symptoms suggestive of adrenal insufficiency/steroid withdrawals to their medical team. Recent practice for pediatric patients with GIAI who have a peak cortisol between 350 and 429 nmol/L (12.7-15.6 µg/dL) is to treat with sick days rules only. Patients who failed the SST with a peak cortisol <350 nmol/L (<12.7 µg/dL) continued on physiological glucocorticoid replacement and received standardized education on steroid sick day rules, on administration of intramuscular hydrocortisone and were given a British Society for Pediatric Endocrinology & Diabetes (BSPED) steroid emergency card.[16] They were monitored using EMC usually done every 3 months, to guide timing of subsequent SSTs. Adult patients who passed the SST were weaned 1 mg every 2 to 4 weeks until completely stopped. This approach is taken to counteract withdrawal symptoms in patients even with normal adrenal function.[17] All patients who came off their glucocorticoids were advised to monitor their symptoms and given an emergency glucocorticoid prescription to cover intercurrent illness for 6 to 12 months after stopping glucocorticoids.[18] Those who failed the test were given standard education on sick day rules and intramuscular hydrocortisone and monitored via a dedicated steroid clinic with EMC used to guide timing of subsequent SSTs, which were usually done every 3-6 months.

Short synacthen test protocol

Endocrine nurse specialists carried out the SSTs on a dedicated investigation unit in both the pediatric and adult hospitals. The protocol for the SST involves administration of intravenous or intramuscular Synacthen (Atnahs Pharma UK Limited, Essex, UK) (145 µg/m^2 for pediatric patients and 250 µg for adults) and measurement of plasma adrenocorticotrophic hormone (ACTH) and serum cortisol at 0 min and serum cortisol at 30 min. The SST was performed ~24 h after the last prednisolone dose and patients on hydrocortisone or/and inhaled glucocorticoids were asked to omit the dose the evening before and the morning of the SST until the test was completed. A pass SST was defined as post-ACTH 30-min cortisol of ≥430 nmol (≥15.6 µg/dL) for both cohorts.[19,20] Measurement of serum cortisol in the pediatric cohort was conducted using Vitros 5600 (Ortho Clinical Diagnostics analyser, New York, USA) interassay precision coefficient of variation (CV) 4.1% to 5%. The serum cortisol was measured using Elecsys Cortisol II assay (*Roche* Diagnostics GmbH, Mannheim, Germany) (Cobas® interassay precision CV 1.1% to 5.5%) in the adult cohort. ACTH samples were immediately packed in ice and transported to the laboratory within 10 min of collection. ACTH levels were measured

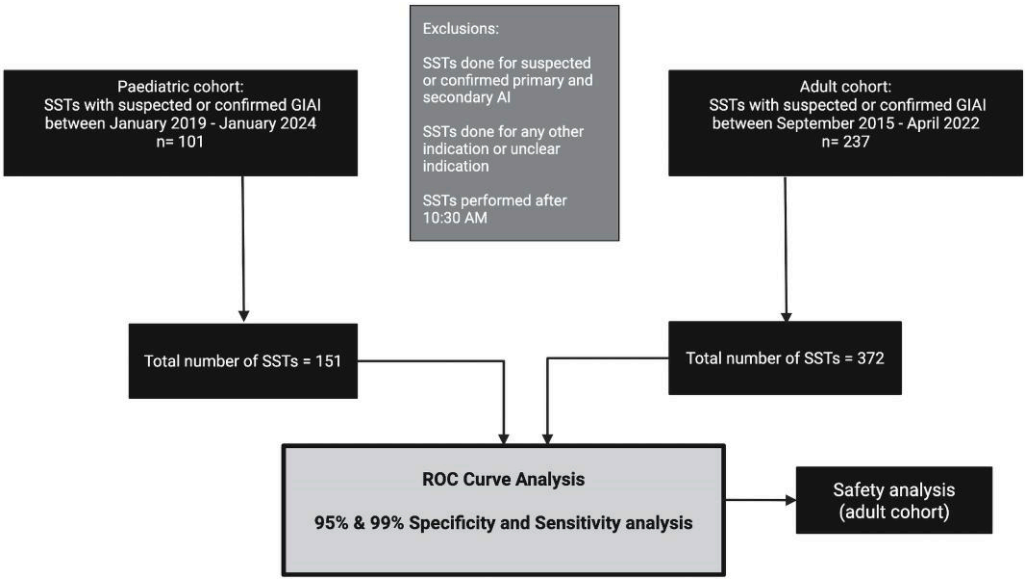


Figure 1. Flowchart demonstrating the study design (created with biorender.com). AI, adrenal insufficiency; GIAI, glucocorticoid-induced adrenal insufficiency; ROC, receiver operator characteristic; SST, short synacthen test.

using Siemens Immulite 2000 chemiluminescent assay (Siemens, Frimley, United Kingdom interassay precision CV 6.1% to 10.0%) in both cohorts.

Data/statistics

Demographic, clinical and laboratory data for all those in the study were extracted from patient case notes. The diagnostic performance of morning cortisol, ACTH and cortisol:ACTH ratio to predict a pass SST was determined via receiver operating characteristic (ROC) curve analysis by plotting true positive rate (sensitivity) against the false-positive rate (1-specificity) for all results in the dataset. The area under curve (AUC) was reported with associated 95% confidence intervals (CIs). Cut offs with 95% and 99% sensitivity for each variable predicting a pass on SST were identified. Likewise, 95% and 99% specificity cut offs for morning cortisol, ACTH and cortisol:ACTH ratio were determined to predict a fail on SST.

To compare if 95% or 99% cut offs should be chosen for predicting a pass SST in clinical practice, outcomes of all adult patients with results falling in between the 2 cut-offs were examined for successful glucocorticoid weaning, mortality and number of hospital admissions in the 12 months following weaning of glucocorticoids. Sensitivity analyses comparing EMC values before and after 9 AM, and those on and without opioids were also conducted.

All the data were recorded in password-protected Excel spreadsheets and stored securely on hospital computers in line with national governance protocols. Continuous variables are represented as mean and standard deviation (SD) for normally distributed data, and as median and inter-quartile range [IQR] for non-normally distributed data, while categorical variables are represented by the number of cases (n) and a percentage (%) of the total. The data were analysed using SPSS version 27.

Approvals

The study was registered with both Trusts' Clinical Audit & Effectiveness Units (Sheffield Children's Trust, reference number SE1825; Sheffield Teaching Hospitals, reference number 10195) as an institutional case note review. All data collected as part of this project reflected routine clinical care and therefore a formal ethical approval was not required. The study was conducted in accordance with the principles set out in the Declaration of Helsinki. No funding was required. The study has been reported in line with the STROBE statement for observational studies.[21]

Results

In the pediatric cohort, 151 SSTs from 101 patients were identified over the 5-year study period, 48 (31.8%) SSTs reach the threshold for a pass. In the adult cohort, 372 SSTs were included, performed on 237 patients, 136 (36.6%) of which were a pass. Most patients in the pediatric cohort were only on oral glucocorticoids $n = 109$ (72.2%), in contrast to the adult cohort where most ($n = 229$) were on combined oral and inhaled glucocorticoids (61.6%). Underlying haematological (24.5%) and respiratory (23.2%) etiology were the main reason for steroid treatment and SST testing in the pediatric cohort, while in the adult cohort, respiratory etiology alone accounted for 58.9% of the SSTs. The flowchart for the study design is summarized in Figure 1 and the baseline demographics and clinical features of the final number of patients included in the study are described in Table 1.

ROC curve analysis and cut offs

ROC curve analysis of morning cortisol, ACTH and cortisol:ACTH ratio is summarized in Figure 2 for pediatric [A] and adult [B] cohorts. Morning cortisol was the best performing test in both groups, with AUC of 0.79 (95% CI, 0.71, 0.87) in children and 0.88 (95% CI, 0.84, 0.91) in adults. The AUC for cortisol:ACTH ratio and ACTH alone was 0.77 and 0.46 for children and 0.80 and 0.54 for adults, respectively. The 95% morning cortisol cut offs to exclude GIAI were 278 (10.1 μg/dL) and 290 nmol/L (10.5 μg/dL) for the pediatric and adult cohorts respectively. The 95% and 99%

Table 1. Baseline demographics and clinical features of patients in adult and pediatric cohorts included in the study.

	Pediatric cohort	Adult cohort
Number of patients *N*	101	237
Number of SSTs *N*	151	372
Number of Females *n* (%)	49 (48.5%)	146 (61.6%)
Mean Age (SD) (years)	8.6 (5.2)	59.6 (15.1)
Range	[0.3-18.1]	[17.9-87.8]
Number of passed SSTs *n* (%)	48 (31.8%)	136 (36.6%)
Median time of 0 min sample [IQR]	09:11 [09:00- 09:30]	09:35 [09:10-09:50]
Range	08:40-10:30	08:15-10:30
Type of glucocorticoids *n* (%)	Oral + Inhaled = 18 (11.9%) *High dose = 6 (33.3%) Medium dose = 4 (22.2%) Low dose = 8 (44.4%) Oral = 109 (72.2%) Inhaled only = 16 (10.6%) High dose = 3 (18.8%) Medium dose = 9 (56.3%) Low dose =4 (25%) Others = 8 (5.3%) (Topical with or without inhaled or other routes of administration	Oral + Inhaled = 229 (61.6%) High dose = 147 (64.2%) Medium dose = 71 (31.0%) Low dose = 11 (4.8%) Oral = 141 (37.9%) Inhaled only = 2 (0.5%) High dose = 2 (100%)
Etiology *n* (%)	Haematology = 37 (24.5%) Respiratory = 35 (23.2%) Neonatology = 21 (13.9%) Rheumatology = 20 (13.2%) Gastroenterology = 13 (8.6%) Dermatology = 6 (3.9%) Neurology = 5 (3.3%) Others = 14 (9.3%)	Respiratory = 219 (58.9%) Rheumatology = 76 (20.4%) Haematology = 31 (8.3%) Oncology = 16 (4.3%) Endocrinology = 8 (2.2%) Gastroenterology = 8 (2.2%) Dermatology =7 (1.9%) Others = 7 (1.9%)
Number of SSTs while taking opioids *n* (%)	8 (5.3%)	50 (13.4%)

Abbreviations: IQR, Interquartile range; SD, Standard deviation; SST, Short synacthen test.
*Dose calculated as per National Institute of Clinical Excellence (NICE) clinical knowledge summaries (available via link: https://cks.nice.org.uk/topics/asthma/prescribing-information/inhaled-corticosteroids/#:~:text=More than 800 micrograms budesonide, be considered a low dose).

sensitivity and specificity cut offs of all 3 parameters to predict a pass and fail on SST for both groups are summarized in the Table 2.

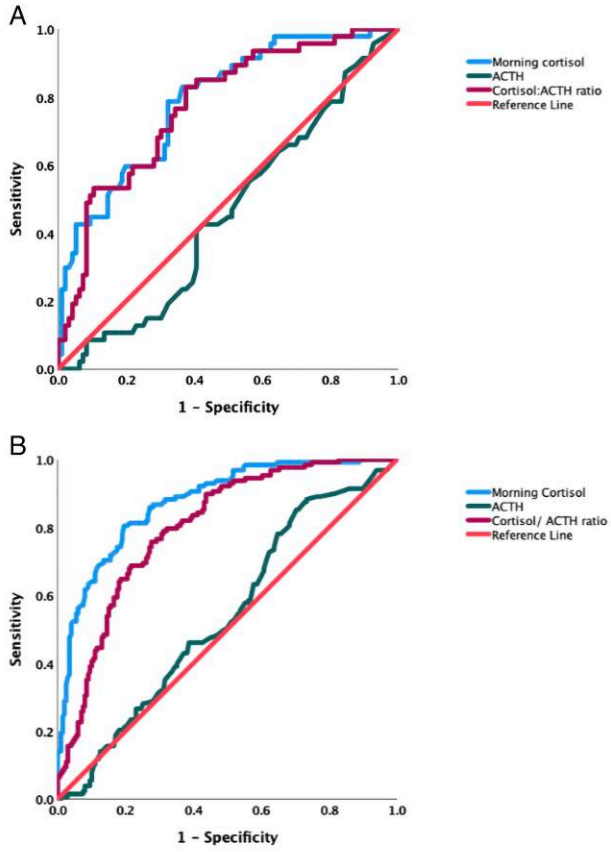
Comparison of 95% and 99% sensitivity EMC cut offs to predict pass SST in the adult cohort

Of the 372 SSTs performed in our adult cohort, 51 patients had morning cortisol results between 290 nmol/L (10.5 µg/dL) and 349 nmol/L (12.7 µg/dL), the 95% and 99% sensitivity cut offs calculated, of whom 82% ($n = 42$) passed their SST. Of the remaining 9 patients, 6 had a borderline 30-min SST cortisol result, between 396 nmol/L (14.4 µg/dL) and 429 nmol/L (15.5 µg/dL), and were successfully weaned off glucocorticoids over the next 8-12 weeks. The remaining 3 patients were not weaned off glucocorticoids: 2 due to their relatively lower 30-min SST cortisol levels (340 nmol/L (12.3 µg/dL) and 380 nmol/L (13.8 µg/dL)) and one due to complex symptoms and health-related issues (chronic fatigue syndrome/myalgic encephalomyelitis) (Table 3). The total glucocorticoid weaning rate in these patients during the period studied was therefore 94% (48/51). The total rate of false negative results for using 95% and 99% EMC cut offs to predict pass SST was 3.4% and 2.8%, respectively. During the 12-month period post-SST, there were no deaths and 2 hospital admissions, both of which were unrelated to AI. There were also no reported cases of adrenal crisis or AI-related hospital admissions for children who were weaned off glucocorticoids.

Using 95% sensitivity and specificity cut offs to predict a pass or fail SST, 68 (45%) SSTs in the pediatric cohort and 215 (58%) SSTs in the adult cohort could have been avoided.

Discussion

The study results show that morning cortisol performs better than ACTH and cortisol:ACTH ratio in predicting SST outcome in children and adults on glucocorticoids. For children and adults, the morning cortisol cut offs to predict a pass on SST were 278 (10.1 µg/dL) and 290 nmol/L (10.5 µg/dL) at 95% sensitivity, and 316 nmol/L (11.5 µg/dL) and 349 nmol/L (12.7 µg/dL) at 99% sensitivity, respectively. Using a 95% sensitivity cut off, 278 nmol/L (10.1 µg/dL) in children and 290 nmol/L (10.5 µg/dL) in adults can be used to wean off glucocorticoids with appropriate education. However, if morning cortisol readings are low (115 nmol/L [4.2 µg/dL] and 133 nmol/L [4.8 µg/dL] respectively), then adrenal insufficiency is likely, and a confirmatory SST can be avoided. In our pediatric and adult cohorts 45% and 58% of SSTs could have been avoided using these cut offs. Based on our study findings, we propose using morning cortisol to aid safe and timely cessation of steroids in pediatric and adult patients (Figure 3), with specific thresholds derived for local assays.



	Area under curve (AUC) Children	95% Confidence intervals	Area under curve (AUC) Adults	95% Confidence intervals
Morning Cortisol	0.788	0.711 - 0.865	0.876	0.838 - 0.913
ACTH	0.458	0.360 – 0.555	0.540	0.477 – 0.603
Cortisol: ACTH ratio	0.774	0.695 – 0.894	0.801	0.754 – 0.849

Figure 2. Receiver operating characteristic (ROC) curve analysis of morning cortisol, ACTH and cortisol:ACTH ratio in [A] pediatric and [B] adult cohorts.

Serum cortisol values are usually measured in nmol/L and µg/dL. The cut-offs recommended by the joint ESE/ES guidelines are 300 and 150 nmol/L, and 10.0 µg/dL and 5 µg/dL respectively, which are not exactly equivalent (calculated equivalent values would be 10.9 and 5.4 µg/dL).[6] Our proposed cut offs of 278/290 nmol/L (10.1/10.5 µg/dL) and 115/133 nmol/L (4.2/4.8 µg/dL) provide support for the recommended values. NICE also suggests the same cut offs of 300 nmol/L and 150 nmol/L to predict adrenal sufficiency and insufficiency.[7] The cut offs derived from our study of children and adults provide supporting evidence for the thresholds recommended in these guidelines during weaning of glucocorticoids.

Several studies have reported EMC cut offs to predict the SST outcome in the adult general population.[22–24] However, there is scarcity of studies examining this in patients on glucocorticoids for a non-endocrine indication using a contemporary immunoassay (Table 4). Results for most assays are comparable to ours. Sbardella *et al.*[25] compared the cut offs between different assays in another study. The reported cut offs from Roche immunoassay ($n = 404$), were 331 nmol/L (12.0 µg/dL) and 386 nmol/L (14.0 µg/dL) for reported 95% and 99% specificity to pass the SST. However, cortisol values were measured using a slightly older first-generation assay which would explain reported higher readings compared with ours, as values using second generation assays are lower.[26,27] In addition to immunoassays, we have reviewed our serum cortisol data analysed on LC-MS/MS from a previously published glucocorticoid cohort ($n = 139$).[28] We found that in this cohort, the 95% sensitivity cut off to predict adrenal sufficiency was ≥299 nmol/L (≥10.8 µg/dL), while the 95% specificity to fail the SST was <135 nmol/L (<4.9 µg/dL) (AUC 0.91 95% CI, 0.86, 0.96), both comparable with the results reported here. There are some studies examining the role of EMC using low dose SST in children[29] but there are no studies examining the role of EMC in predicting SST outcome during glucocorticoid weaning in children.

Studies evaluating morning cortisol cut-offs have reported a range of sensitivities and specificities between 80% and

Table 2. 95% and 99% specificity and sensitivity cut offs predicting to pass and fail SST in [A] pediatric and [B] adult cohorts.

[A]	95% sensitivity to exclude GIAI (corresponding specificity)	99% sensitivity to exclude GIAI (corresponding specificity)	95% specificity to confirm GIAI (corresponding sensitivity)	99% specificity to confirm GIAI (corresponding sensitivity)
Morning cortisol	278 nmol/L (43%) 10.1 μg/dL	316 nmol/L (23%) 11.5 μg/dL	115 nmol/L (37%) 4.2 μg/dL	20 nmol/L (8%) 0.7 μg/dL
ACTH	88 ng/L (0%) 19.4 pmol/L	151 ng/L (0%) 33.3 pmol/L	4.5 ng/L (8%) 1.0 pmol/L	3.5 ng/L (6%) 0.8 pmol/L
Cortisol: ACTH ratio	20.3 (21%)	37.3 (9%)	3.4 (29%)	2.3 (13%)
[B]	**95% sensitivity to exclude AI (corresponding specificity)**	**99% sensitivity to exclude AI (corresponding specificity)**	**95% specificity to confirm AI (corresponding sensitivity)**	**99% specificity to confirm AI (corresponding sensitivity)**
Morning cortisol	290 nmol/L (55%) 10.5 μg/dL	349 nmol/L (24%) 12.7 μg/dL	133 nmol/L (48%) 4.8 μg/dL	89 nmol/L (35%) 3.2 μg/dL
ACTH	87 ng/L (2%) 19.2 pmol/L	135 ng/L (1%) 29.7 pmol/L	6.5 ng/L (7%) 1.4 pmol/L	3.5 ng/L (1%) 0.8 pmol/L
Cortisol: ACTH ratio	19.2 (18%)	24.0 (0%)	4.5 (40%)	3.0 (25%)

Abbreviations: GIAI, glucocorticoid-induced Adrenal insufficiency.

Table 3. Summary of patients ($n = 9$) with basal cortisol between 290 nmol/L and 349 nmol/L (10.5 and 12.7 μg/dL) and 30-minute cortisol <430 nmol/L (<15.6 g/dL) in adult cohort.

Patient number	0-min cortisol (nmol/L)	30-min cortisol (nmol/L)	Glucocorticoids weaned (Yes/No)	AI-related hospital admissions	All hospital admissions	Further comments
1	297	340	No	0	0	Two further failed SSTs 8 and 18 months later
2	323	380	No	0	0	Passed repeat SST 9 months later
3	297	396	Yes	0	0	
4	346	399	Yes	0	1	
5	304	399	Yes	0	0	Glucocorticoids stopped but re-started after another exacerbation of asthma
6	325	401	No	0	0	Remains on glucocorticoids due to complex symptomatology (chronic fatigue syndrome/myalgic encephalomyelitis)
7	298	402	Yes	0	0	
8	337	420	Yes	0	1	
9	347	429	Yes	0	0	

Table 4. Summary of all studies examining morning cortisol cut offs to pass or fail short synacthen test in patients on glucocorticoids.

Study	Study population	Assay	Cut offs reported
Sagar *et al.*[40]	$n = 238$ Adults only Rheumatology only	Siemens ADVIA Centaur	100% specificity to pass SST: 350 nmol/L (12.7 μg/dL) 100% sensitivity to fail SST: 100 nmol/L (3.6 μg/dL)
Sbardella *et al.*[25]	$n = 40$ Adults and children >11 years old	Siemens ADVIA Centaur	95% and 100% specificity to pass SST: 272 nmol/L (9.9 μg/dL) and 323 nmol/L (11.7 μg/dL) 100% sensitivity to fail SST: 211 nmol/L (7.6 μg/dL)
	$n = 32$ Adults	Abbott Architect	100% specificity to pass SST: 336 nmol/L (12.2 μg/dL) 100% sensitivity to fail SST: 124 nmol/L (4.5 μg/dL)
	$n = 404$ Adults	Roche (1st generation)	95% and 99% specificity to pass SST: 331 nmol/L (12.0 μg/dL) and 386 nmol/L (14.0 μg/dL)
Tomkins *et al.*[41]	$n = 67$ Adults Post- kidney transplant	Roche (2nd generation)	100% specificity to pass SST: 288 nmol/L (10.4 μg/dL)
Diddhenipothage *et al.*[32]	$n = 137$ Adults	Abbott Architect i-2000	100% specificity to pass SST: 376 nmol/L (13.6 μg/dL)

Abbreviations: SST, Short synacthen test.

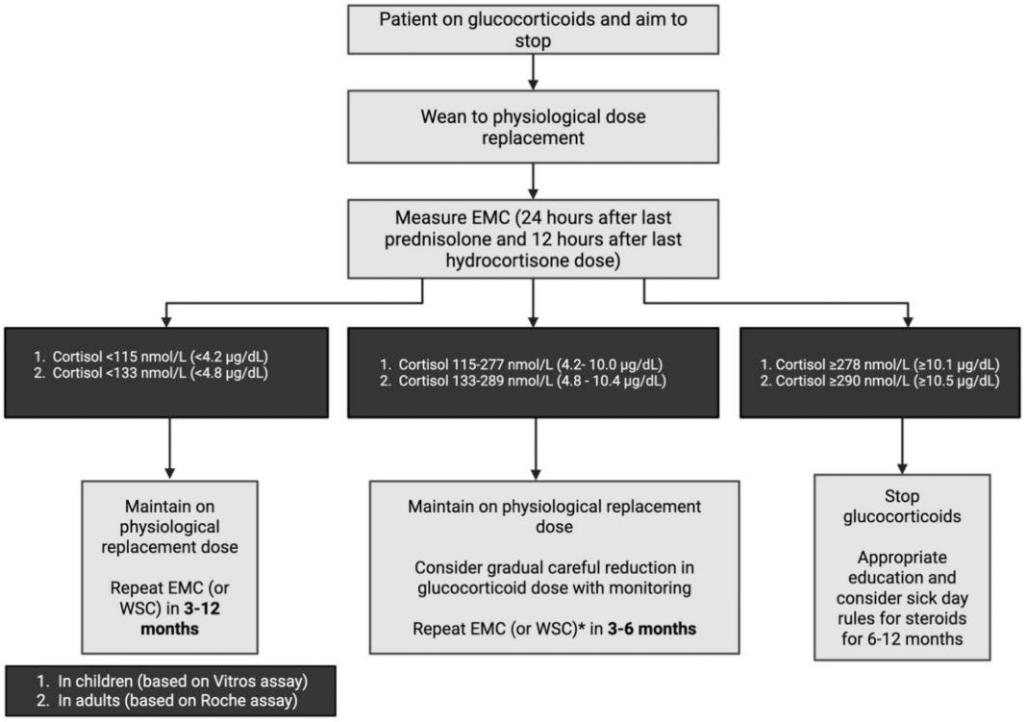


Figure 3. Flowchart summarizing a proposed approach to discontinue glucocorticoid therapy.

100%,[23,25,30–32] with 95% and 99% cut offs being the most widely reported. For most biochemical measurements, the 5th and 95th percentiles (2 standard deviations from the mean) are used,[33] however for some eg, high sensitive troponin, 1st and 99th percentile (3 standard deviations from mean) are recommended.[34] No such consensus exists for morning cortisol. Using 99% cut offs would result in lower false negative rates than 95% but the latter may be more suitable for screening purposes. In this study, we followed up adult patients for 12 months after they were weaned off glucocorticoids and confirmed no AI-related hospital admissions or deaths, suggesting that 95th cut off readings can be used cautiously with appropriate patient education. There were also no AI-related hospital admissions or deaths in the pediatric cohort after weaning off glucocorticoids.

ACTH is checked at 0 min on an SST by some clinicians to predict adrenal status.[10] 0 min ACTH is also used to distinguish between primary and secondary/tertiary AI.[14] In patients on supraphysiological doses of glucocorticoids, ACTH secretion from the pituitary gland is suppressed.[5] When supraphysiological exogenous glucocorticoids are discontinued ACTH levels are reported to recover first followed by resumption of cortisol production.[35] In our clinical practice ACTH has been used on a case-by-case basis to guide physicians in identifying reactivation of the HPA axis,[5] but, strong evidence behind this approach is lacking. Our group has recently developed a multivariable model to predict the outcome of the next SST using baseline and 30-min cortisol readings from the previous SST ($n = 175$ patients with sequential SSTs, including $n = 109$ with tertiary AI).[36] We found that the addition of basal ACTH did not improve the predictive model. In our study here, the cortisol:ACTH ratio was 77% predictive of the SST outcome, possibly suggesting a dynamic relationship between changes in cortisol and ACTH as the HPA axis is reactivating. However, we did not find additional value of cortisol:ACTH over EMC alone.

The major clinical risk while weaning glucocorticoids is adrenal crisis which has a reported mortality of up to 6%.[37] The reported incidence of adrenal crises in AI patients is 5-10 per 100 patient years.[37] When following our adult patients with morning cortisol between 290 nmol/L and 349 nmol, there were 2 non-AI related admissions and no deaths. The risk of adrenal crisis is thought to be lower in those with GIAI due to an intact renin angiotensin aldosterone system and residual cortisol production.[38,39] Nevertheless, it is important to ensure that all patients with GIAI receive standard sick day rules education.[18]

In patients with equivocal or borderline results ie, between lower and higher cut-offs, the guidelines suggest monitoring with morning cortisol after a few weeks or months.[6] In a patient with equivocal results, one can either wean the glucocorticoids with patient education on sick day rules and how to identify symptoms of adrenal insufficiency or gradually reduce the glucocorticoid dose and continue to monitor clinically and biochemically using EMC or waking salivary cortisone (WSC).[28] If a patient develops symptoms of AI, the dose will need to be increased back to the pre-symptomatic dose or, if stopped, re-started, and slower weaning recommended. Although the ESE/ES guidelines do not recommend routine use of the SST, an alternative approach in patients with equivocal results is to immediately proceed to a SST in this group. 30% (25/84) of children and 36% (56/157) of the adult patients in our study passed the SST and were weaned off glucocorticoids raising the question whether the SST could expedite the weaning process when compared with using a serum cortisol. This approach may have a role when it is difficult to wean patients off glucocorticoids, especially if they are presenting with withdrawal symptoms and need reassurance.

The main limitation of the study is its retrospective design. We would recommend validation in a prospective study. The ESE/ES and NICE guidelines recommend cortisol sampling

to be undertaken early between 8 and 9 AM to capture the circadian cortisol peak while our patients were asked to attend for testing between 8 AM and 10:30 AM. A separate analysis in adults comparing EMC values before and after 9 AM demonstrated that EMC taken before 9 AM cut offs were slightly higher than those taken after 9 AM, as expected, however, there was not a significant impact on the overall results and the difference in cut offs are comparable within the limits of CV% of the assays (Table S1). Few SSTs were performed while the participants were on opioids which can reduce EMC levels. However, main etiology of AI was glucocorticoid-induced in these patients and a sensitivity analysis excluding these patients did not influence the results (Table S2). Furthermore, we only have data for patients on glucocorticoids who were referred to endocrinology for assessment of their HPA axis, whereas many patients are managed within their speciality.

In conclusion, this is the first study to derive morning cortisol cut offs for both children and adults weaning from glucocorticoids using 2 different modern immunoassays. Our cut offs provide further evidence in support of the recommendations from ES/ESE and NICE guidelines. These cut-offs should be harmonized with clinical practice to reduce the number of SSTs required. The study also shows that measurement of ACTH with cortisol routinely with all SSTs does not help predict the SST outcome and therefore is only required to investigate the etiology of adrenal insufficiency when it is unknown.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Muhammad Fahad Arshad (Conceptualization [equal], Data curation [lead], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Visualization [equal], Writing—original draft [lead], Writing—review & editing [equal]), Aneeq Ahmed (Data curation [equal], Writing—review & editing [supporting]), Sian Beddows (Data curation [supporting], Writing—review & editing [supporting]), Isaac Marsh (Data curation [supporting], Writing—review & editing [supporting]), Arwa Mullamitha (Data curation [supporting], Writing—review & editing [supporting]), John Newell-Price (Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Richard Ross (Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), Charlotte Elder (Conceptualization [equal], Data curation [supporting], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Supervision [supporting], Validation [supporting], Writing—original draft [supporting], Writing—review & editing [equal]), and Miguel Debono (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Project administration [equal], Supervision [lead], Validation [equal], Writing—original draft [equal], Writing—review & editing [equal]).

Conflict of interest

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Data availability

The data supporting study findings are available within the manuscript. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Broersen LH, Pereira AM, Jørgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2015;100(6):2171-2180. https://doi.org/10.1210/jc.2015-1218
2. Laugesen K, Jørgensen JOL, Petersen I, Sørensen HT. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. *Eur J Endocrinol*. 2019;181(3):267-273. https://doi.org/10.1530/EJE-19-0305
3. Luo X, Yu S, Zeng Z, *et al*. Systemic glucocorticoid prescriptions pattern and factors of inappropriate use in primary care institutions of Southwest China. *Front Public Health*. 2022;10:952098. https://doi.org/10.3389/fpubh.2022.952098
4. Abu Bakar K, Khalil K, Lim YN, *et al*. Adrenal insufficiency in children with nephrotic syndrome on corticosteroid treatment. *Front Pediatr*. 2020;8:164. https://doi.org/10.3389/fped.2020.00164
5. Prete A, Bancos I. Glucocorticoid induced adrenal insufficiency. *BMJ*. 2021;374:n1380. https://doi.org/10.1136/bmj.n1380
6. Beuschlein F, Else T, Bancos I, *et al*. European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-induced Adrenal Insufficiency. *J Clin Endocrinol Metab*. 2024;109(7):1657-1683. https://doi.org/10.1210/clinem/dgae250
7. National Institute for Health and Care Excellence. Adrenal insufficiency: identification and management [NG243]. Accessed July 1, 2025. www.nice.org.uk/guidance/NG243.
8. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet*. 1988;1(8596):1208-1210. https://doi.org/10.1016/S0140-6736(88)92020-X
9. Sherlock M, Stewart PM. The short synacthen test and its utility in assessing recovery of adrenal function in patients with central adrenal insufficiency. *J Clin Endocrinol Metab*. 2019;104(1):17-20. https://doi.org/10.1210/jc.2018-01317
10. Cross AS, Helen Kemp E, White A, *et al*. International survey on high- and low-dose synacthen test and assessment of accuracy in preparing low-dose synacthen. *Clin Endocrinol (Oxf)*. 2018;88(5):744-751. https://doi.org/10.1111/cen.13559
11. Abjörn C, Leonhardt T. [Anaphylactic shock with fatal outcome after injection of synthetic corticotropin (Synacthen Depot) in a patient with severe asthma]. *Lakartidningen*. 1970;67(39):4364-4366.
12. Grossman AB. Society for endocrinology position statement on the use of synthetic acth (Synacthen) in patients with a history of asthma. Accessed July 1, 2025. https://www.endocrinology.org/media/2712/sfe-synacthen-position-statement-2018.pdf.
13. Arshad MF, Elder C, Newell-Price J, Ross R, Debono M. A retrospective study on weaning glucocorticoids and recovery of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab*. 2024;109(11):e2031-e2037. https://doi.org/10.1210/clinem/dgae059
14. Butt MI, Alzuhayri N, Riazuddin M, Bakhsh AMK. The short synacthen test: variations in methodology and protocols in KSA. *J Taibah Univ Med Sci*. 2022;17(4):596-601. https://doi.org/10.1016/j.jtumed.2022.01.010

15. Elder CJ, Sachdev P, Wright NP. The short Synacthen test: a questionnaire survey of current usage. *Arch Dis Child*. 2012;97(10):870-873. https://doi.org/10.1136/archdischild-2012-301713
16. Mushtaq T, Ali SR, Boulos N, *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):871-878. https://doi.org/10.1136/archdischild-2022-325156
17. Hansen SB, Dreyer AF, Jorgensen NT, *et al*. Changes in adrenal function and insufficiency symptoms after cessation of prednisolone. *JAMA Netw Open*. 2025;8(3):e251029. https://doi.org/10.1001/jamanetworkopen.2025.1029
18. Simpson H, Tomlinson J, Wass J, Dean J, Arlt W. Guidance for the prevention and emergency management of adult patients with adrenal insufficiency. *Clin Med (Lond)*. 2020;20(4):371-378. https://doi.org/10.7861/clinmed.2019-0324
19. Husni H, Abusamaan MS, Dinparastisaleh R, Sokoll L, Salvatori R, Hamrahian AH. Cortisol values during the standard-dose cosyntropin stimulation test: personal experience with Elecsys cortisol II assay. *Front Endocrinol (Lausanne)*. 2022;13:978238. https://doi.org/10.3389/fendo.2022.978238
20. El-Farhan N, Pickett A, Ducroq D, *et al*. Method-specific serum cortisol responses to the adrenocorticotrophin test: comparison of gas chromatography-mass spectrometry and five automated immunoassays. *Clin Endocrinol (Oxf)*. 2013;78(5):673-680. https://doi.org/10.1111/cen.12039
21. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499. https://doi.org/10.1016/j.ijsu.2014.07.013
22. Yo WS, Toh LM, Brown SJ, Howe WD, Henley DE, Lim EM. How good is a morning cortisol in predicting an adequate response to intramuscular synacthen stimulation? *Clin Endocrinol (Oxf)*. 2014;81(1):19-24. https://doi.org/10.1111/cen.12373
23. Kumar R, Carr P, Wassif W. Diagnostic performance of morning serum cortisol as an alternative to short synacthen test for the assessment of adrenal reserve; a retrospective study. *Postgrad Med J*. 2022;98(1156):113-118. https://doi.org/10.1136/postgradmedj-2020-138514
24. Mackenzie SD, Gifford RM, Boyle LD, Crane MS, Strachan MWJ, Gibb FW. Validated criteria for the interpretation of a single measurement of serum cortisol in the investigation of suspected adrenal insufficiency. *Clin Endocrinol (Oxf)*. 2019;91(5):608-615. https://doi.org/10.1111/cen.14071
25. Sbardella E, Isidori AM, Woods CP, *et al*. Baseline morning cortisol level as a predictor of pituitary-adrenal reserve: a comparison across three assays. *Clin Endocrinol (Oxf)*. 2017;86(2):177-184. https://doi.org/10.1111/cen.13232
26. Grassi G, Morelli V, Ceriotti F, *et al*. Minding the gap between cortisol levels measured with second-generation assays and current diagnostic thresholds for the diagnosis of adrenal insufficiency: a single-center experience. *Hormones (Athens)*. 2020;19(3):425-431. https://doi.org/10.1007/s42000-020-00185-y
27. Kline GA, Buse J, Krause RD. Clinical implications for biochemical diagnostic thresholds of adrenal sufficiency using a highly specific cortisol immunoassay. *Clin Biochem*. 2017;50(9):475-480. https://doi.org/10.1016/j.clinbiochem.2017.02.008
28. Debono M, Elder CJ, Lewis J, *et al*. Home waking salivary cortisone to screen for adrenal insufficiency. *NEJM Evid*. 2023;2(2):EVIDoa2200182. https://doi.org/10.1056/EVIDoa2200182
29. Laulhe M, Dumaine C, Chevenne D, *et al*. Glucocorticoid induced adrenal insufficiency in children: morning cortisol values to avoid LDSST. *Front Pediatr*. 2022;10:981765. https://doi.org/10.3389/fped.2022.981765
30. Woods CP, Argese N, Chapman M, *et al*. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. *Eur J Endocrinol*. 2015;173(5):633-642. https://doi.org/10.1530/EJE-15-0608
31. Ravindran R, Carter JL, Kumar A, *et al*. Pre-test cortisol levels in predicting short synacthen test outcome: a retrospective analysis. *Clin Med Insights Endocrinol Diabetes*. 2022;15:11795514221093316. https://doi.org/10.1177/11795514221093316
32. Diddhenipothage SAD, Beck KJ, Loo H, *et al*. "A morning cortisol is the most effective clinical predictor of short synacthen test outcome": a tertiary care centre experience. *Clin Endocrinol (Oxf)*. 2023;99(2):142-151. https://doi.org/10.1111/cen.14934
33. Yalla N, Bobba G, Guo G, Stankiewicz A, Ostlund R. Parathyroid hormone reference ranges in healthy individuals classified by vitamin D status. *J Endocrinol Invest*. 2019;42(11):1353-1360. https://doi.org/10.1007/s40618-019-01075-w
34. Sandoval Y, Apple FS, Mahler SA, *et al*. High-sensitivity cardiac troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines for the evaluation and diagnosis of acute chest pain. *Circulation*. 2022;146(7):569-581. https://doi.org/10.1161/CIRCULATIONAHA.122.059678
35. Graber AL, Givens JR, Nicholson WE, Island DP, Liddle GW. Persistence of diurnal rhythmicity in plasma acth concentrations in cortisol-deficient patients. *J Clin Endocrinol Metab*. 1965;25(6):804-807. https://doi.org/10.1210/jcem-25-6-804
36. Lawrence NR, Arshad MF, Pofi R, *et al*. Multivariable model to predict an ACTH stimulation test to diagnose adrenal insufficiency using previous test results. *J Endocr Soc*. 2023;7(12):bvad127. https://doi.org/10.1210/jendso/bvad127
37. Hahner S, Spinnler C, Fassnacht M, *et al*. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *J Clin Endocrinol Metab*. 2015;100(2):407-416. https://doi.org/10.1210/jc.2014-3191
38. Rushworth RL, Chrisp GL, Torpy DJ. GLUCOCORTICOID-INDUCED ADRENAL INSUFFICIENCY: A STUDY OF THE INCIDENCE IN HOSPITAL PATIENTS AND A REVIEW OF PERI-OPERATIVE MANAGEMENT. *Endocr Pract*. 2018;24(5):437-445. https://doi.org/10.4158/EP-2017-0117
39. Li D, Brand S, Hamidi O, *et al*. Quality of life and its determinants in patients with adrenal insufficiency: a survey study at 3 centers in the United States. *J Clin Endocrinol Metab*. 2022;107(7):e2851-e2861. https://doi.org/10.1210/clinem/dgac175
40. Sagar R, Mackie S, Morgan AW, Stewart P, Abbas A. Evaluating tertiary adrenal insufficiency in rheumatology patients on long-term systemic glucocorticoid treatment. *Clin Endocrinol (Oxf)*. 2021;94(3):361-370. https://doi.org/10.1111/cen.14405
41. Tomkins M, Martin-Grace J, Kennedy C, *et al*. Adrenal insufficiency is common amongst kidney transplant recipients receiving maintenance prednisolone and can be predicted using morning cortisol. *Nephrol Dial Transplant*. 2023;38(1):236-245. https://doi.org/10.1093/ndt/gfac044