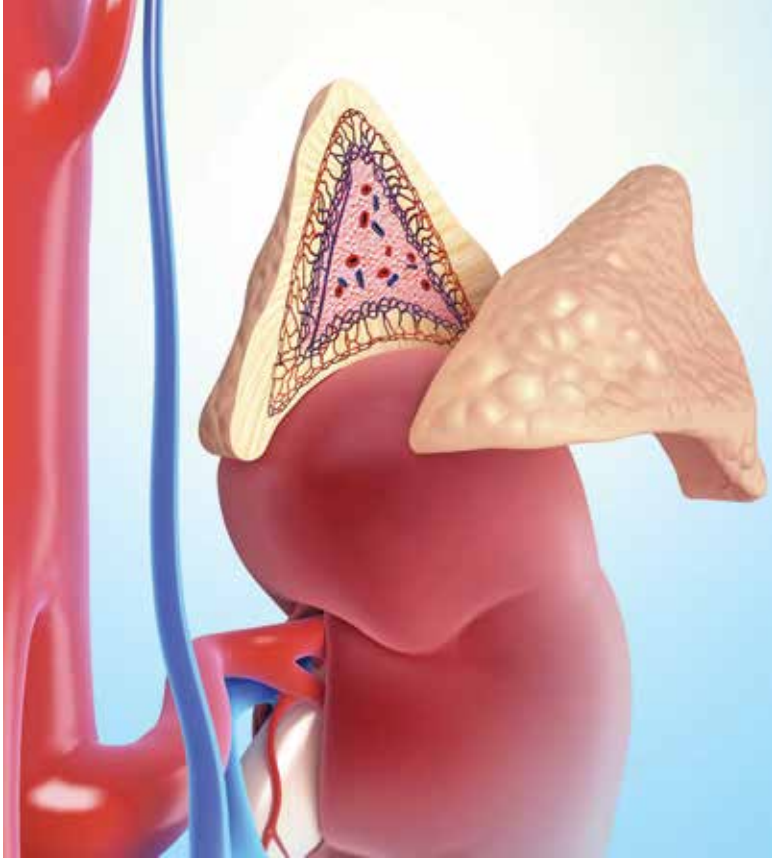

Addison's disease

Managing 'sick days' to avoid crises

MARNI A. NENKE MB BS, BSci
DAVID J. TORPY MB BS, PhD, FRACP

Integral to the body's stress system, an increase in cortisol levels is critical to surviving illness. Timely administration of exogenous glucocorticoids in doses designed to mimic this response is essential in preventing an episode of adrenal insufficiency or crisis in patients who lack their own cortisol, such as in those with Addison's disease.

Key points

- **Glucocorticoid replacement should reflect physiological cortisol production.**
- **Patients with adrenal insufficiency require additional supplementation in times of medical or surgical stress, with doses proportionate to the degree of the challenge severity.**
- **The maximum daily production of cortisol during stress is 100 mg/m² per day. Doses in excess of 200 to 300 mg hydrocortisone or equivalent glucocorticoid are unwarranted and have potential risks.**
- **Education is key in preventing adrenal crises and is the responsibility of all medical practitioners.**

ENDOCRINOLOGY TODAY 2014; 3(1): 26-31

Dr Nenke is the AR Clarkson Research Fellow at the Endocrine and Metabolic Unit, Royal Adelaide Hospital. Professor Torpy is Deputy Director at the Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, SA.

Addison's disease is a rare condition that requires life-long hormone replacement. When homeostasis is threatened by stressors, including infection, trauma or surgery, cortisol production temporarily increases. Failure to increase cortisol can result in an adrenal crisis, a life-threatening complication. Many cases of adrenal crisis can be prevented with pre-emptive corticosteroid supplementation. The management of Addison's disease remains controversial and there are no universal guidelines for steroid supplementation during medical or surgical stress. Current recommendations for glucocorticoid replacement aim to reflect normal physiology in both routine and stress conditions.

The hypothalamic–pituitary–adrenal (HPA) axis and cortisol production

Cortisol, a life-sustaining steroid hormone, is produced by the zona fasciculata of the adrenal cortex (see Figure). Diurnal variation results in a cortisol peak at 6 to 9 am and trough at 11 pm to 2 am. Previously, daily cortisol production was estimated at 12 to 15 mg/m² per day, although cortisol replacement in Addison's disease at this dose commonly caused Cushingoid features.[1] More recent analyses suggest that the adrenal gland produces only 5.7 mg/m² of cortisol per day,[1] or the equivalent of about 20 mg oral hydrocortisone[2] when bioavailability, protein binding and clearance are considered.[3] Stress, defined as a threat to homeostasis, such as infection or trauma, may increase cortisol production 10-fold. Key functions of cortisol include: immune modulation; support of catecholamine actions within the cardiovascular system elevating blood pressure and redirecting blood flow to essential organs; metabolic actions such as elevation of blood glucose (hence 'glucocorticoids'); and neurocognitive actions leading to heightened awareness and stress-related behaviour.

Cortisol levels also vary during the day according to stressful stimuli and, in situations of severe stress, the synthesis of cortisol can

increase to up to 100 mg/m^2 per day.[4] The ideal treatment for adrenal insufficiency would be hormone replacement at the identical rate and rhythm of physiological hormone production, although this is yet to be achieved.[5]

Addison's disease

Primary adrenal insufficiency, or Addison's disease, is the failure of the adrenals to produce adequate cortisol and aldosterone. Addison's disease is relatively rare with a prevalence of approximately 100 per million people in white populations. Up to 50% of patients have had signs and symptoms for more than 12 months before the diagnosis of Addison's disease.[6] Early identification of adrenal insufficiency remains a challenge given its rarity, often nonspecific initial symptoms and the gradual progression of autoimmune Addison's disease. Fatigue, postural hypotension, hyperkalaemia, hyponatraemia, weight loss and hyperpigmentation are key features of untreated Addison's disease. The turn of the century has seen a conservative change in the approach to cortisol replacement in these patients. We now aim for patients to be on a lower dose that relieves their symptoms of glucocorticoid deficiency and more closely mimics normal cortisol production rates, for example, 10 to 12 mg/m^2 per day oral hydrocortisone equivalent (see Table 1 for equivalent doses).[7] There has also been a trend towards use of short-acting natural glucocorticoids, such as hydrocortisone (identical to cortisol) or cortisone acetate (readily converted to active hydrocortisone), rather than longer-acting synthetic glucocorticoids, such as prednisolone and dexamethasone. This should prevent metabolic and bone complications caused by over replacement, but may theoretically predispose to under-treatment and therefore increase the risk of an adrenal crisis.[8]

Patients with Addison's disease generally require fludrocortisone (0.05 to 0.3 mg daily) to replace the aldosterone normally produced by the zona glomerulosa in the adrenal glands. Fludrocortisone is available only as an oral preparation. Doses are adjusted to control the hyperkalaemia, hyponatraemia, hypotension and salt hunger that may occur without this hormone. Doses can be fine tuned to normalise the plasma renin activity. During illness, however, although aldosterone levels often rise, the higher doses of hydrocortisone generally prescribed (over 50 mg daily) provide adequate mineralocorticoid support and additional fludrocortisone is not required.

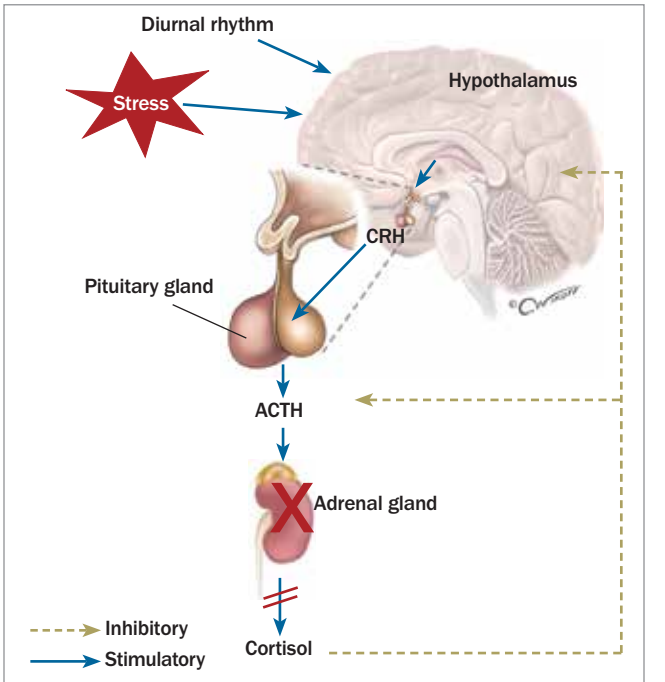

Figure. The hypothalamic–pituitary–adrenal axis and the stress response. Cortisol acts via a negative feedback loop to inhibit both corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). However, in primary adrenal insufficiency, the adrenal gland undergoes degeneration or destruction, resulting in failed cortisol production and therefore loss of negative inhibition on the pituitary and hypothalamus. In situations of stress, the adrenals cannot respond to the increased need for cortisol. Stressors include pain, physical activity, fever, psychic stress, trauma, surgery, hypoglycaemia and hypotension.

Secondary adrenal insufficiency

Deficiency of cortisol may also arise through any destructive process of the pituitary or hypothalamus, leading to a lack of the adrenocorticotropic hormone (ACTH) and/or corticotropin-releasing hormone stimulation that drives cortisol secretion, resulting in secondary adrenal insufficiency. Concomitant thyroid, gonadal and growth hormone deficiencies are common, although aldosterone secretion is intact. More commonly, use of anti-inflammatory doses of glucocorticoids may produce a feedback-induced deficiency of ACTH and cortisol that may persist for six to 18 months after weaning of exogenous glucocorticoids. In secondary adrenal insufficiency, cortisol deficiency is often partial. Adrenal crises are not as common in these situations because the cortisol deficiency is generally not as severe as in Addison's disease. Furthermore, the lack of mineralocorticoid deficiency in secondary adrenal insufficiently renders these patients less prone to dehydration and electrolyte disturbance.

Table 1. Equivalent doses and strengths of common glucocorticoid preparations

Generic name	Brand name	Tablet strength	Approximate bioequivalent dose	Biological half-life (hours)[7]
Dexamethasone	Dexmethsone	0.5 mg and 4 mg	0.5 mg	36 to 72
Prednisolone	Predsolone, Panafcortelone, Solone	1 mg, 5 mg and 25 mg	5 mg	12 to 36
Hydrocortisone	Hysone	4 mg and 20 mg	20 mg	8 to 12

1. Key strategies in adrenal crisis prevention

- Encourage and emphasise the importance of compliance to the patient
- Review of symptoms for under-replacement
- Implement a sick day management plan for the patient
- Ensure patient has a MedicAlert tag and medical identification card
- Ensure patient carries a self-injector emergency hydrocortisone kit
- Ensure patient has an annual endocrinologist review
- Advise patients to consider annual influenza vaccination

Adrenal crisis prevention

An adrenal crisis is a life-threatening complication of Addison's disease that requires emergency treatment. In healthy subjects, stressors including illness, trauma or surgery will result in increased cortisol production by the adrenal glands. Patients with Addison's disease are unable to meet the increased demand for cortisol and develop acute signs of adrenal insufficiency, including anorexia, weakness, abdominal pain, vomiting and unexplained fever. Severe hypovolaemic hypotension occurs as a result of mineralocorticoid deficiency. Hyperkalaemia, hyponatraemia, hypercalcaemia, hypoglycaemia, raised creatinine and anaemia are common laboratory findings. An adrenal crisis will be the presenting complaint in half of patients eventually diagnosed with Addison's disease[6] and still contributes to the increased mortality seen in patients with Addison's disease.[9] Adrenal crises in people with primary adrenal insufficiency occur at a rate of 6.6 per 100 patient years, with the risk being higher in those with comorbidities.[9] Most crises in patients with known Addison's disease occur because of failure to implement sick day management strategies during illness, particularly gastroenteritis, by patients or doctors, or because of glucocorticoid dose reduction, cessation or nonadherence. Thus many cases of acute adrenal crises in patients with known adrenal insufficiency may be avoided if the patient and doctor had promptly implemented the prevention strategies.

Adjustments to medications including dosages and timing should be well communicated and glucocorticoid replacement should never be stopped. All treating doctors should be informed of incidents in which extra steroids are required and of threatened or actual adrenal crises.

The primary care doctor plays an important role in preventing adrenal crises (see Box 1). When the GP reviews a patient with known adrenal insufficiency, enquiring about symptoms of cortisol under-replacement, including weight loss, fatigue, nausea, myalgia and lack of energy, can be helpful to identify patients at risk of an adrenal crisis. Unfortunately, no laboratory measurements are validated for assessing the adequacy of glucocorticoid replacement, and these assessments are made clinically. Adjusting glucocorticoid dose to normalise plasma ACTH will lead to marked glucocorticoid excess with Cushingoid features, due to a lack of normal feedback timing to the hypothalamic–pituitary unit, invalidating this strategy. All patients should have a written 'sick day management plan' and this should be revised and updated at each visit. Patients and their families should receive regular crisis prevention training, including understanding the precipitants, signs, symptoms and management of adrenal crises. A MedicAlert pendant should be worn at all times by the patient. It is also useful for patients to carry the emergency assist card, supplied by MedicAlert that states the condition, medication names and contact numbers of treating doctors, and emergency management instructions. It is pertinent to be aware that patients with Addison's disease caused by autoimmune adrenalitis frequently develop other autoimmune conditions, particularly hyperthyroidism, which can precipitate an acute adrenal crisis. Thyroid hormone excess results in an increased demand for cortisol due to increased cortisol metabolism, therefore increasing the potential for adrenal insufficiency. Measurement of serum thyroid-stimulating hormone level should be performed annually or as clinically indicated. Steroid requirement may increase in patients with untreated coeliac disease. Patients should be referred to the Australian Addison's Disease Association Inc (http://addisons.org.au) for information and support. GPs can also source patient information packs, emergency treatment letters and emergency cards from this website. Annual influenza vaccination is also recommended for patients with Addison's disease.

Emergency self-injector kits are recommended for patients remote from prompt medical care who can arrange for a person to be trained in the intramuscular injection technique. Other patients who wish to have the independence of self-mandated intramuscular injections for emergencies may also be prescribed 100 mg hydrocortisone sodium succinate. The technique for emergency injection is described in a webpage produced by the UK Addison's Disease Self Help Group (www.addisons.org.uk/info/emergency/solucortefguide.html). An instructional video is available on the Australian Addison's Disease Association Inc website (www.addisons.org.au) although access requires membership subscription. Recently, a small, open-label crossover study of patients with stable Addison's disease in Germany found that compared with intramuscular injection, subcutaneous administration of 100 mg hydrocortisone showed no difference between maximal serum cortisol concentrations although there was a minor delay in time to reach target levels.[10] Participants preferred subcutaneous to intramuscular administration. Further work is required to ensure adequate cortisone absorption from subcutaneous injection in unwell patients; however, subcutaneous administration may be a feasible treatment option in the future.

Sick day management

The rationale of sick day management is to predict when the body may require extra cortisol due to increased medical stress. Recommendations are generally based on expert opinion. For mild illness, for example, viral upper respiratory tract infection or uncomplicated urinary infection, we recommend using the 3 x 3 rule,[7] which is tripling the usual oral dose for three days or for the duration of the illness, after which the patient returns to their usual dose (see Box 2). For practical purposes, this often means use of 20 mg hydrocortisone oral three-times daily (or equivalent glucocorticoid). Illness duration greater than three days requires medical review for consideration

2. Example of sick day management plan to be provided to patients

I am taking steroids for adrenal insufficiency. This medication MUST NOT BE STOPPED.

My current dose of hydrocortisone is 10 mg at 8 am and 10 mg at 4 pm.

In the event of fever or mild illness, I will triple my dose to 20 mg three times a day for up to THREE days, then return to my normal dose.

In cases of vomiting or diarrhoea, severe illness, or where oral medications can not be taken, I will need 100 mg IV/IM hydrocortisone administered by a healthcare professional.

GP name _____
Contact number _____
Endocrinologist name _____
Contact number _____

of further investigation or treatment (e.g. with antibiotics), and continued steroid supplementation.

In cases of diarrhoea or vomiting, when oral medication cannot be absorbed, patients will need to seek medical attention, usually at the emergency department for 50 mg intravenous hydrocortisone immediately, followed by 25 mg eight-hourly. In severe illness, for example, pancreatitis, myocardial infarction or sepsis, patients should receive the equivalent of 50 mg intravenous hydrocortisone six-hourly until the condition stabilises.[11] If there is a delay in being able to access medical care, patients or their relatives should administer emergency self-injector kits.

Compared with traditional higher doses, 200 mg/day hydrocortisone appears to be immunomodulatory rather than immunosuppressive.[12,13] An intravenous infusion of 10 mg hour (240 mg/day) hydrocortisone[13] and 50 mg intravenous hydrocortisone every six hours[14] both result in cortisol levels of more than 3000 nmol/L, well above the mean 880 nmol/L seen in patients with septic shock.[15] Therefore, higher doses, even in the setting of severe stress are unwarranted and unphysiological.

Patients taking exogenous glucocorticoids may also require sick day supplementation if their dose is more than 5 mg prednisolone or equivalent per day. The patient's usual dose of glucocorticoids and severity of the illness can be used to estimate the expected cortisol needs of the patient.

As infection is a leading cause of adrenal crises, prompt and thorough management of infectious illness is needed in these patients. Returning to the usual dose of glucocorticoids promptly after resolution of the precipitant will help to avoid over-replacement.

Psychic stress increases cortisol secretion markedly but generally briefly. Cases of adrenal crises precipitated by such stress have been reported.[9] Generally, increased glucocorticoid administration is not required for such times, but some patients with Addison's disease find 24 to 48 hours of increased glucocorticoids helpful under these conditions.[16]

Periprocedural management

Surgical stress is a powerful activator of the HPA axis. Corticotropin-releasing hormone, ACTH and cortisol all rise during surgery, although the extent depends on the type and duration of surgery and anaesthesia used.[17] Cortisol production rates can increase by up to 10-fold under such severe stress, although cortisol levels return to the normal range by 48 hours postoperatively.[4] Thus patients with Addison's disease require corresponding additional steroid cover around the time of an operation. Surgical procedures carried out in patients with Addison's disease without sufficient steroid cover was the cause of 6% of adrenal crises experienced in one series.[8] Therefore, steroids given perioperatively need to be sufficient to cover the cortisol requirements of the surgery, but not so great as to potentially impair wound healing, cause hyperglycaemia or encourage infection.

Over 60 years ago, two cases of adrenal crises due to withdrawal of preoperative glucocorticoids were reported. This prompted the recommendation that steroids be administered in large doses during the perioperative period, and this became the standard of care for the next half a century.[18] Experimental data now suggest that this is excessive when compared with the normal cortisol response to surgery stress, and lower doses for a shorter period are now recommended. Estimated cortisol production rates in response to surgery are as follows: 25 mg/day for minor surgery; 50 to 75 mg/day for moderate surgery; and 100 to 150 mg/day for major surgery (hydrocortisone equivalents).[18] Our suggested perioperative steroid cover, extrapolated from these estimates and in general agreement with other published recommendations, are shown in Table 2.[2,7,19,20,21] These suggestions do not take into account postoperative complications, for example, infection, which deserves reassessment of cortisol needs and requires longer steroid cover.

Patients taking less than 5 mg prednisolone or equivalent per day, unless recently weaned, may have an intact HPA axis and do not require glucocorticoid supplementation with stress, but a conservative policy may be to treat as though they are taking higher doses.[2,21] Some authors suggest that all patients treated with exogenous glucocorticoids should be treated empirically with stress doses of steroids,[2,22] others advocate preoperative testing of the HPA axis,[18] and others still suggest that the patient's usual therapeutic steroid dose is sufficient and stress dosing is not required.[23] In the absence of large clinical trials to guide us in this matter, a reasonably safe and cost-effective approach would be for patients to continue their usual dose of corticosteroid (an equivalent dose of intravenous hydrocortisone can be given if fasting). Additional cover should only be given according to Table 2 if the proposed operation is likely to elicit a stress response that is not covered by the patient's usual dose.[18] For example, a patient taking 20 mg oral prednisolone daily (equivalent to 80 mg hydrocortisone) would not require additional cover for minor or moderate surgery (expected cortisol response <75 mg/day), but would require additional cover for major surgery.

Equivalent hydrocortisone doses by infusion may be needed in some clinical situations where variation in glucocorticoid levels may

Table 2. Medication requirements for surgical procedures in patients with Addison's disease

Type of procedure	Perioperative needs	Postoperative needs
Surgery[2,7,19,20]		
• Major surgery with long recovery time e.g. cardiothoracic surgery, oesophagectomy, Whipple's procedure	50 mg hydrocortisone IV with induction (at time anaesthetic given)	Continue 50 mg hydrocortisone IV every 8 hours for 24 hours. Taper to normal dose over 2 to 3 days
• Moderate surgery e.g. open cholecystecomy, total joint replacement, hysterectomy, Caesarean section. Includes dental surgery under general anaesthetic	25 mg hydrocortisone IV with induction	Hydrocortisone 25 mg IV 8-hourly for 24 hours. Then return to normal oral dose
• Minor surgery e.g. cataract surgery, hernia repairs, laparoscopy with local anaesthetic, endoscopy includes dental surgery with >1 hour local anaesthetic	25 mg hydrocortisone with induction	Usual replacement dose
Labour and vaginal birth[7]	25 mg hydrocortisone IV at onset of labour then 6-hourly until delivery 100 mg IV at time of delivery	Double oral dose for 24 to 48 hours after delivery
Invasive bowel procedures requiring laxatives[21] e.g. colonoscopy, barium enema	Hospital admission overnight with IV fluids and 100 mg hydrocortisone IV during purgative stages of preparation. 100 mg hydrocortisone IV at induction	20 mg hydrocortisone oral 8-hourly then return to normal dose

have a clinical effect, generally after a loading dose of 50 mg intravenous hydrocortisone.

Conclusion

Identified treatment goals for healthcare providers who are managing patients with Addison's disease are as follows: provision of physiological glucocorticoid replacement; improvement in patient quality of life; and avoidance of adrenal crisis.[5] Timed-release and modified-release oral glucocorticoid preparations, subcutaneous hydrocortisone infusions and provision of dehydroepiandrosterone are strategies that have been investigated to address the former goals. Prevention of adrenal crises is possible with use of stress dosing and/or parenteral use of glucocorticoids in patients with illness or inability to take oral steroids, respectively. **ET**

References

1. Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72: 39-45.
2. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002; 287: 236-240.
3. Peacey SR, Guo CY, Robinson AM, et al. Glucocorticoid replacement therapy: are patients over treated and does it matter? Clin Endocrinol (Oxf) 1997; 46: 255-261.
4. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997; 337: 1285-1292.
5. Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol 2013; 169: R165-R175.
6. Zelissen PM. Addison patients in the Netherlands: medical report of the survey. Dutch Addison Society, The Hague, The Netherlands; 1994.
7. Nieman L. Treatment of adrenal insufficiency in adults. In: Lacroix A, ed. UpToDate. Waltham, MA: Wolters Kluwer; 2013.
8. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. Eur J Endocrinol 2010; 162: 115-120.
9. Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol 2010; 162: 597-602.
10. Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. Eur J Endocrinol 2013; 169: 147-154.
11. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008; 36: 1937-1949.
12. Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. Intensive Care Med 2008; 34: 344-349.
13. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of 'low-dose' hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003; 167: 512-520.
14. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab 2006; 91: 3725-3745.
15. Ho JT, Al-Musalhi H, Chapman MJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab 2006; 91: 105-114.
16. Quinkler M, Hahner S. What is the best long-term management strategy for patients with primary adrenal insufficiency? Clin Endocrinol (Oxf) 2012; 76: 21-25.
17. Jabbour SA. Steroids and the surgical patient. Med Clin North Am 2001; 85: 1311-1317.
18. Salem M, Tainsh RE, Jr., Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994; 219: 416-425.
19. Jung C, Inder WJ. Management of adrenal insufficiency during the stress of medical illness and surgery. Med J Aust 2008; 188: 409-413.
20. Addison's Clinical Advisory panel. Glucocorticoid medication requirements for surgery and dentistry. ADSHG; 2011.
21. LaRochelle GE, Jr, LaRochelle AG, Ratner RE, Borenstein DG. Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisone. Am J Med 1993; 95: 258-264.
22. Krasner AS. Glucocorticoid-induced adrenal insufficiency. JAMA 1999; 282: 671-676.
23. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Arch Surg 2008; 143: 1222-1226.

COMPETING INTERESTS: None.