Guidelines

Management of glucocorticoids for patients with adrenal insufficiency during the peri-operative period

Association of Anaesthetists of Great Britain and Ireland, Royal College of Physicians and Society for Endocrinology UK

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Support acknowledgement

This research was supported by the National Institute for Health Research (NIHR) through the Birmingham and Oxford NIHR Biomedical Research Centres.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Summary

These guidelines aim to ensure that patients with adrenal insufficiency are both identified and adequately supplemented with glucocorticoids during the peri-operative period. There are two major categories of adrenal insufficiency. Primary adrenal insufficiency is due to diseases of the adrenal gland (failure of the hormone-producing gland), and secondary adrenal insufficiency is due to deficient adrenocorticotropin hormone secretion by the pituitary gland, or deficient corticotropin releasing hormone secretion by the hypothalamus (failure of the regulatory centres). Patients taking physiological replacement doses of corticosteroids for either primary or secondary adrenal insufficiency are at significant risk of adrenal crisis, and must be given stress doses of hydrocortisone during the peri-operative period.

Many more patients other than those with adrenal and hypothalamic-pituitary causes of adrenal failure are receiving glucocorticoids as treatment for other medical conditions. Daily doses of prednisolone of 5 mg or greater in adults and 15 $mg.m^{-2}$ hydrocortisone-equivalent or greater in children may result in hypothalamic-pituitary-adrenal axis suppression if administered for one month or more by oral, inhaled, intranasal, intra-articular or topical routes; this chronic administration of glucocorticoids is the most common cause of secondary adrenal suppression, sometimes referred to as tertiary adrenal insufficiency. A pragmatic approach to adrenal replacement during major stress is required, considering the evidence available; blanket recommendations would not be appropriate, and it is essential for the clinician to remember that adrenal replacement dosing in stress is in addition to usual steroid treatment.

Patients with previously undiagnosed adrenal insufficiency sometimes present for the first time following the stress of surgery. Anaesthetists must be familiar with the symptoms and signs of acute adrenal insufficiency, so that inadequate supplementation or undiagnosed adrenal insufficiency can be detected and treated promptly. Delays may prove fatal.

Recommendations

- Prescribed glucocorticoid therapy (prednisolone ≥5mg per day or hydrocortisone-equivalent dose of 15 $mg.m^{-2}$ per day), across all routes of administration (oral, inhaled, topical, intranasal, intra-articular), can cause suppression of the hypothalamo-pituitary adrenal axis, and is the most common cause of adrenal insufficiency that anaesthetists will encounter.

- All glucocorticoid-dependent patients are at risk of adrenal crisis as a consequence of surgical stress or illness, and it is essential to be able to recognise and diagnose this medical emergency. If in doubt about the need for glucocorticoids, they should be given, as there are no long-term adverse consequences of short-term glucocorticoid administration.

- Patients with a long-standing diagnosis of adrenal insufficiency are often well-informed about their disease. Anaesthetists should enquire closely about the patient's history of glucocorticoid self-management, any previous episodes of adrenal crisis, and how practised they are at medication adjustments for illness, injury or postoperative recovery. Best practice is to collaborate as far as possible with the patient's endocrinologist when planning scheduled surgery, and when caring for post-surgical cases.

- Hydrocortisone 100 mg by intravenous injection should be given at induction of anaesthesia in adult patients with adrenal insufficiency from any cause, followed by a continuous infusion of hydrocortisone at 200 $mg.24h^{-1}$, until the patient can take double their usual oral glucocorticoid dose by mouth. This regimen is preferred above others due to enhanced safety. This should then be tapered over time to the appropriate maintenance dose, in most cases within a week. Intramuscular administration may be prescribed in circumstances where intravenous infusion therapy is impractical (See Tables 1-3 for details).

- Major complications and critical illness excite a prolonged stress response. Any glucocorticoid supplementation should reflect this pattern.

- Dexamethasone is not adequate as glucocorticoid treatment in patients with primary adrenal insufficiency, as dexamethasone has no mineralocorticoid activity.

- Children with adrenal insufficiency are more vulnerable to problems with glycaemic control than adults, and require frequent blood glucose monitoring. They can be treated either with a bolus of hydrocortisone at induction followed by an immediate continuous infusion of hydrocortisone, or alternatively with a bolus at induction followed by subsequent four hourly intravenous boluses of hydrocortisone in the postoperative period. Detailed recommendations based on age and body weight are presented in the main text. The period of fasting should be minimized and adrenal insufficient patients should be prioritized on routine surgical operating lists.

- Maternal glucocorticoid supplementation in obstetric patients with adrenal insufficiency represents another group who require special mention; women may require a higher maintenance dose during the later stages of pregnancy (20^{th} week onwards), and stress dose supplementation using hydrocortisone 100mg at the onset of labour, and then either by continuous intravenous infusion of hydrocortisone 200 $mg.24h^{-1}$ or 50mg intramuscularly every six hours until after delivery.

This is a consensus document produced by members of a Working Party established by the Association of Anaesthetists, the Society for Endocrinology UK (SfE), the Royal College of Physicians (RCP) and the Royal College of Anaesthetists (RCoA). It has been seen and approved by the Association and RCoA Board of Directors, and the RCP Executive.

What other guideline statements are available on this topic?

In 2005, the Addison's Self Help Group published 'Surgical guidelines for Addison's Disease and other forms of adrenal insufficiency', authored by its Clinical Advisory Panel [1]. In 2010 these guidelines were endorsed by NICE Clinical Knowledge Summaries. A Cochrane Intervention Review 'Supplemental perioperative steroids for surgical patients with adrenal insufficiency' was first published in 2009 and revised in 2012, before being withdrawn in 2012, as the evidence base was very poor and limited in size and quality, focusing mainly on minor dental procedures [2]. A European Expert Consensus Statement for diagnosis, treatment and follow-up of patients with primary adrenal insufficiency endorsed the Addison's Clinical Advisory Panel surgical guidelines in 2013 [3]. A recent review paper on the management of adrenal insufficiency made

recommendations for the prevention and treatment of adrenal crisis, but with little detail applicable to the peri-operative setting [4]. A new Steroid Emergency card has been developed for distribution to patients across Europe, with a UK version available online, with a link to a detailed management guidelines for adrenal crisis (https://www.endocrinology.org/clinical-practice/clinical-guidelines/adrenal-crisis/), and also available in print [5]. The Endocrine Society USA has recently released a new clinical guideline, focusing on primary adrenal insufficiency [6], with detailed recommendations on stress dosing both in the adult patient and the paediatric setting.

Why was this guideline developed?

The Association of Anaesthetists of Great Britain and Ireland (AAGBI), the Society for Endocrinology UK, the Royal College of Anaesthetists and the Royal College of Physicians received a 'Rule 43' letter (now known as a 'Report to Prevent Future Deaths' - https://www.judiciary.gov.uk/related-offices-and-bodies/office-chief-coroner/pfd-reports/) from HM Coroner Sheffield in 2012, expressing concern about standards of care for patients with adrenal insufficiency undergoing surgery. Professors Wass and Arlt responded on behalf of the Royal College of Physicians with an editorial in the *British Medical Journal* [7]. The AAGBI and the Royal College of Anaesthetists welcomed the opportunity to work with the Addison's Clinical Advisory Panel to deliver this updated Consensus National Guidance.

How and why does this statement differ from existing guidelines?

This is the first national guidance on the topic that integrates expertise in endocrinology with the practicalities of anaesthetic and surgical services delivery, and addresses the needs of both adults and children.

The patients' perspective

Patients with a long-standing diagnosis of adrenal insufficiency are often well informed about their disease, and may be more informed than their anaesthetist regarding treatment options. Other patients will have little knowledge of their need for supplementary peri-operative glucocorticoids, and may adopt a more passive approach to their medication management. Anaesthetists should enquire closely about the patient's history of steroid self-management, any previous episodes of adrenal crisis, and how practised they are at medication adjustments for illness, injury or postoperative recovery.

Physiology

Cortisol is the dominant glucocorticoid in humans and is produced in the zona fasciculata of the adrenal cortex. Release is pulsatile and follows a circadian rhythm, such that the reference range for plasma cortisol is 140–700 nmol.l^{-1} at 0900, but only 80–350 nmol.l^{-1} at midnight [8]. Cortisol production and release is controlled by adrenocorticotropic hormone (ACTH), released from the anterior pituitary gland, which is in turn controlled by corticotropin releasing hormone (CRH) from the hypothalamus. Up to 20 mg of cortisol is released each day. Cortisol is lipophilic, and therefore highly protein bound in the plasma to cortisol-binding globulin (60–80%) and albumin (15–35%). The free active fraction is small, usually around 5%. Following uncomplicated major elective surgery there is a proportionate increase in pro-inflammatory cytokines, CRH, ACTH and cortisol. A five-fold increase in secretion, to about 100 mg of cortisol per day, is common. Plasma cortisol concentration typically returns to baseline within 24–48 h [9,10]. During protracted critical illness, reduced metabolism and clearance contribute to hypercortisolaemia [11].

Prevalence of adrenal insufficiency in adult and paediatric populations

Primary adrenal insufficiency relates to conditions where the underlying aetiology lies within the adrenal gland itself, and includes conditions such as Addison's disease (autoimmune adrenal insufficiency) and congenital adrenal hyperplasia. Patients will frequently be deficient in the production of both cortisol and aldosterone. Patients with secondary adrenal insufficiency due to pituitary or hypothalamic disorders are deficient in cortisol, but continue to secrete aldosterone in response to renin.

Seven in 1000 people are prescribed long-term oral corticosteroid therapy, approximately 100 times the number with intrinsic deficiency, creating a large population at risk of adrenal crisis [12]. Prescribed glucocorticoid therapy, across all routes of administration (oral, inhaled, topical, intranasal, intra-articular), can cause suppression of the hypothalamo-pituitary adrenal axis (sometimes referred to as tertiary adrenal insufficiency) [13, 14]. Inhaled corticosteroid therapy is very common, and whilst it has been claimed not to endanger the functioning of the hypothalamic pituitary adrenal axis when administered within recommended dose ranges, recent evidence has shown that suppression of the adrenal response to ACTH is common [4, 15, 16]. Furthermore, it can occur at commonly prescribed doses and in a dose-dependent manner. Importantly, all steroid-dependent patients are at risk of adrenal crisis [17. The prevalence of adrenal insufficiency in children is generally unknown, but glucocorticoid treatment for disorders such as asthma, renal

disease, inflammatory conditions such as juvenile chronic arthritis and inflammatory bowel disease, and Duchenne's muscular dystrophy accounts for a significant proportion of cases. A recent Canadian study suggested an incidence of 0.35/100000 (Goldbloom et al. Arch Dis **Child**. 2017 Apr;102(4):338-339). Primary adrenal insufficiency affects 1 in 8-10,000 children with congenital adrenal hyperplasia being the commonest cause and occurring in 1 in 15,000 live births. Secondary adrenal insufficiency due to ACTH deficiency affects approximately 1 in 10000 children, and can be due to either congenital causes such as developmental disorders of the hypothalamus and pituitary or acquired causes such as brain tumours and their treatment.

Clinical outcome in patients with adrenal insufficiency and risk of adrenal crisis

In a cohort of 1675 Swedish patients with adrenal insufficiency, the risk ratio for all-cause mortality was 2.19 for men and 2.86 for women, with narrow confidence intervals. Excess mortality in both men and women was attributable to cardiovascular, malignant and infectious diseases [18]. Adrenal crises requiring hospital treatment occur about 6-8 times per 100 patient years among patients with primary or secondary adrenal insufficiency due to adrenal and hypothalamic-pituitary disease, respectively. In a recent British survey, 8.6% of patients with chronic adrenal insufficiency reported a previous adrenal crisis caused by insufficient glucocorticoid medication during an inpatient stay, e.g. for elective surgery [19]. While some of these cases were related to inadequate dosing, others were due to medication errors and omissions on the wards.

In the only prospective study to date, the incidence of adrenal crisis in a cohort of 423 patients with primary and secondary adrenal insufficiency was 8.3 per 100 replacement years, and two patients died during adrenal crisis during a 2-year follow-up [20].

Around half of the patients affected by adrenal crisis report a previous crisis, usually precipitated by gastroenteritis or fever, but also caused by surgical episodes, pregnancy, emotional distress and other wide-ranging triggers [21, 22]. Patients with comorbidities are more vulnerable to adrenal crisis, notably those with asthma and diabetes. Patients with mineralocorticoid or vasopressin dependency are also less stable than secondary adrenal patients with intact mineralocorticoid function [19]. It is vital that physiological replacement therapy is not interrupted, and that the daily dose is increased at times of physiological stress. We recommend hydrocortisone 100 mg intravenously at the start of surgery, followed by an infusion of 200 $mg.24h^{-1}$. If recovery is uncomplicated, we recommend doubling the regular oral replacement dose of hydrocortisone for a week before the maintenance dose is resumed (e.g. if the usual replacement dose was 10-5-5

mg hydrocortisone, this would be doubled to 20-10-10 mg for a week post-operatively, assuming the patient is recovering well). However, if the patient remains unwell and in critical care, then stress dose cover by continuous intravenous infusion should be continued. Many patients with a longstanding diagnosis are accustomed to managing their condition, and report that ward nursing staff may dismiss their observations about warning signs of under-replacement during illness or following surgery. The fact that adrenal crisis symptoms and signs can occur in physiologically stressed patients while plasma cortisol levels are normal, or even high, is recognised in the concept of relative adrenal insufficiency.

Patients receiving therapeutic glucocorticoids

In general, there is little or no conclusive evidence on which to base recommendations in this population. A daily glucocorticoid dose equivalent to prednisolone ≥ 5 mg, for longer than one month, represents an adrenal suppressive dose in a proportion of adults [3, 4].

Marik and Varon undertook a systematic review of the relevant literature up to 2008 [24]. The data were limited; they identified only two small, randomised controlled trials and six prospective cohort studies. The groups were heterogeneous, as were the outcomes reported. Some studies identified reduced adrenal responsiveness, and the imposed surgical stress varied considerably. No glucocorticoids were administered for 48 h either before or after surgery in some of the studies. There were only isolated instances of volume-resistant hypotension, and the authors argued that there was no evidence to support the routine administration of corticosteroids in doses higher than the therapeutic dose. Similarly, Gibbison, Angelini and Lightman advised that in the absence of evidence that higher peri-operative doses of glucocorticoids improve haemodynamic and mortality outcomes, they were 'probably not required' [8].

There are data from case series of short synacthen tests performed in populations receiving therapeutic corticosteroid treatment of between 5–20 mg prednisolone daily. These report a variable number of patients (approximately one third to a half) not achieving the target cortisol concentration when 5 mg or more of prednisolone was administered [17]. Whilst a precise dose-response relationship could not be demonstrated, these data serve to highlight that a dose of prednisolone 5 mg (or standard dose inhaled glucocorticoids) can be associated with inadequate adrenal cortisol reserve in a significant number of patients.

Given the risks of an inadequate glucocorticoid response (and the lack of long-term harm related to supplementation), we support balanced, individualised glucocorticoid supplementation in addition to ongoing treatment during the peri-operative period (and by extension whenever

patients are subjected to any physiological stress), in this group of patients. A number of factors need to be considered, including dose, duration, treated condition and the degree of physiological stress. Individual patients may thus either need no supplementation, a single dose, or a regimen delivered over a number of days. These considerations are discussed, and broad recommendations made in Tables 1–3. It is clear that if in doubt about the need for glucocorticoids, they should be given, as there are no long-term adverse consequences of short-term glucocorticoid administration.

Pharmacology

Therapeutic glucocorticoids include hydrocortisone (structurally identical to cortisol), prednisolone and dexamethasone. They vary in their immunosuppressive and metabolic properties; 10 mg hydrocortisone is roughly equivalent to 2.0 mg prednisolone and to 0.1 mg dexamethasone. All have excellent bioavailability orally, and are rapidly absorbed. Dexamethasone is frequently administered to prevent postoperative nausea and vomiting, often in doses of up to 8 mg. This actually equates to 800 mg of hydrocortisone in the form of a long-acting glucocorticoid, and is more than adequate to cover most situations for 24 h. It is important to remember that dexamethasone has no mineralocorticoid activity and, therefore, dexamethasone is inadequate as glucocorticoid stress cover in patients with primary adrenal insufficiency.

The plasma elimination half time of exogenously administered hydrocortisone is approximately 90 min, but may be shorter in patients taking inducers of liver enzyme CYP3A4 [4] or suffering from hyperthyroidism, and longer in critically-ill patients [11]. The volume of distribution of cortisol/hydrocortisone may also be increased. Hydrocortisone is administered parenterally in the peri-operative period until normal enteral function returns. The traditional routes of administration are either via intramuscular injection or intravenous infusion. Recent experiments have established the superiority of intravenous infusion for maintaining plasma cortisol concentrations seen in a normal stress response [25]. We recommend this method of administration when delivering postoperative supplementation [4]. Intramuscular administration has a long tradition of safety and clinical effectiveness, and may be prescribed in circumstances where intravenous infusion therapy is impractical.

Some experts are of the opinion that the dose of hydrocortisone administered should be higher in patients taking drugs that induce CYP3A4, and in obese adults. There is little hard evidence to guide practice, but published cases of peri-operative adrenal crisis are available [26]. We recommend that clinicians maintain a high index of suspicion for adrenal crises in these patients,

and be prepared to immediately increase the dose if necessary. Such patients should preferably be commenced on a continuous infusion of hydrocortisone to reduce the risks of decompensation.

Etomidate administration rapidly and powerfully suppresses cortisol production by inhibiting 11-beta-hydroxylase that catalyses the final step in cortisol biosynthesis [27]. There are inconclusive data and conflicting opinions regarding the advisability of steroid supplementation in patients who receive a single induction dose of etomidate before major or high-risk surgery [28]. Detailed investigation of the response of adrenal steroids to a single dose of etomidate in vivo did not suggest clinically relevant changes [29]. However, adverse outcomes have been identified in patients receiving longer-term etomidate infusions in critical care (now rare) [30]. Again, clinical judgement is required.

Surgical stress

Insufficient cortisol production during a surgical stress response leads to progressive loss of vasomotor tone, and alpha-adrenergic receptor responses to noradrenaline are impaired. Unless the stress is very transient, ongoing reductions in vascular tone lead to orthostatic hypotension, followed by supine hypotension and finally shock, which will be fatal if not rapidly corrected. A tendency to water retention and hyponatraemia induced by anti-diuretic hormone is very common after surgery, and thus patients with insufficient aldosterone production will be particularly susceptible to hyponatraemia.

Surgical stress is not an all or nothing phenomenon. Patient-specific, operative and anaesthetic factors are relevant for determining the level of stress that is associated with the surgical procedure, its severity as well as its preparation and aftercare. The individual response to surgical stress in patients with intact adrenal function is influenced by patient-specific, surgical and anaesthetic factors, as examined by a recent systematic review and meta-analysis, which looked at 71 studies reporting peri-operative cortisol concentrations in almost 3000 individuals. This showed the peri-operative cortisol surge to be most prominent with procedures involving open surgery and general anaesthesia. However, the evidence base was highly heterogeneous and only two of the seven studies employed reference standard mass spectrometry for the measurement of cortisol [10]. Major complications and critical illness excite a prolonged response. Any glucocorticoid supplementation should reflect this pattern.

Features of impending adrenal crisis

Volume-resistant hypotension has long been seen as the cardinal sign of acute adrenal insufficiency, but it may be a late or even agonal event. It is essential to remain vigilant for earlier symptoms and signs. These may include:

- Patient reports of non-specific malaise; somnolence or obtunded conscious level; and cognitive dysfunction. The response to 100 mg of hydrocortisone may be tested.
- Monitoring of vital signs should include sitting (or standing) and supine blood pressure, for early detection of orthostatic hypotension.
- Plasma sodium is often, but not always, low. C-reactive protein may be raised, but this test is of limited value in the postoperative period.
- Persistent pyrexia may be due to adrenal insufficiency, but is usually attributed to postoperative sepsis and treated with antimicrobial chemotherapy. Steroid supplementation should not be reduced or withdrawn while the patient is pyrexial.

It is clear that the short-term use of hydrocortisone supplementation during uncomplicated surgery carries minimal risk. There is a reluctance to use glucocorticoid supplementation too liberally for fear of unwanted side effects. The importance of maintaining peri-operative fluid balance is increasingly accepted, and thus sodium and water retention secondary to supplementation is a potential concern. Glycaemic control is deemed important in diabetic patients and glucocorticoid-induced glycaemia is feared, although it can be easily controlled. The potential negative effect of glucocorticoids on wound healing, increased risk of infection and the increased risk of peptic ulceration are further concerns. Patients with adrenal insufficiency who develop complications of surgery should be managed in the critical care environment.

Working with the patient and their endocrinologist

'Listening to a well-informed adrenal patient who says that he or she need additional steroids, and taking urgent action, will avoid unnecessary deaths from this eminently treatable medical problem.' [5]. Patients may carry a steroid emergency card, and may wear a medical bracelet or necklace [31]. All patients and their close family should have been educated on 'Sick Day Rules', which refer to doubling the dose of steroids during periods of physiological stress, and injecting hydrocortisone either intramuscularly or intravenously in major stress or surgery [4]. However, there are documented instances where a systems failure has seen patients discharged following diagnosis, with little or no education about sick day rules. The anaesthetist should not assume that

patients are fully competent to manage dosage adjustments for the prevention of adrenal crisis during intercurrent illness or injury. Some are provided with hydrocortisone self-administration kits that they may have brought with them to hospital on a precautionary basis [21]. They may bring with them leaflets about surgery and adrenal insufficiency. Best practice is to collaborate as far as possible with the patient's endocrinologist when planning scheduled surgery and when caring for post-surgical cases, especially for patients with multiple risk factors (age, comorbidities). [32]. It is advisable to ensure that the patient has 'first on the list' priority.

Day case surgery considerations

We recommend that patients with adrenal insufficiency having body surface surgery need not be denied day case surgery, but that it is particularly important to ensure they have adequately recovered, and are not suffering from nausea or vomiting, prior to discharge home. They should be instructed to return to hospital should they feel unwell, or develop nausea or vomiting. Laparoscopic surgery as a day case can be considered, but we recommend a '23 hour stay' protocol, where available. Ensure the patient is familiar with the sick day rules for febrile illness [4], has an injection kit in case of vomiting, and that a companion has been trained to use it.

Obstetrics

Adrenal insufficiency is rarely encountered for the first time in pregnancy. Pregnancy itself does not influence the severity of the disease, but may delay the diagnosis as some of the signs and symptoms might be misattributed to the pregnancy itself. Serum total and free cortisol is normally increased 20–40% in pregnancy, so it may be advisable to prescribe a higher maintenance dose for women with adrenal insufficiency in the latter stages of pregnancy [4, 33–34, 35, 36]. The recommendations for peri- and postoperative surgical stress doses are the same in pregnancy as for other adults. During delivery, hydrocortisone 100 mg should be injected with the onset of active labour (contractions every five min for the last hour, or cervical dilation > 4 cm), followed by either continuous infusion of hydrocortisone 200 $mg.24h^{-1}$, or hydrocortisone 50 mg intramuscularly every six h, with rapid tapering (over 1-3 days) to the regular replacement dose after an uncomplicated delivery.

Children

The peri-operative management guidelines for children with adrenal insufficiency are based on the protocols developed at Great Ormond Street Hospital and University College London Hospital,

and cover patients with primary adrenal insufficiency, including congenital adrenal hyperplasia, and those with secondary adrenal insufficiency. The hydrocortisone infusion rates are based on cortisol clearance data.

All adrenal insufficiency patients, both adults and children, should have 'first on the list' priority in order to minimise fasting or dehydration, which they tolerate poorly. Start hourly checks of blood glucose if pre-operative fasting exceeds four hours. No child with adrenal insufficiency should be fasted for more than six hours. The child should continue to take their regular doses of hydrocortisone until the time of surgery; alternatively, the hydrocortisone should be given intravenously. After surgery, blood glucose should be checked every hour until enteral intake is resumed.

All children who have known glucocorticoid deficiency (primary or secondary), or who are at risk of glucocorticoid deficiency (on significant exogenous dose of glucocorticoid), should receive an intravenous dose of hydrocortisone on induction (2 $mg.kg^{-1}$ for major surgery, 1 $mg.kg^{-1}$ if minor surgery under general anaesthesia). Postoperatively, hydrocortisone 2 $mg.kg^{-1}$ should be administered every 4 hours, by either the intravenous or intramuscular route, following major surgery. Alternatively, a hydrocortisone infusion (Table 3) should be administered if there is evidence of instability or sepsis. When enteral intake is established, the patient should receive double the normal dose of hydrocortisone for 48 hours, and this should then be reduced to standard hydrocortisone doses once stability has been achieved. After minor surgery or sedation or general anaesthesia for MRI, the child should receive double the normal doses of hydrocortisone administered orally. Thereafter, the child can be switched to normal daily dosing. For those minor surgical procedures not requiring a general anaesthetic, a double dose of hydrocortisone should be given pre-operatively, followed by normal glucocorticoid doses postoperatively.

Particular care is required in patients who have diabetes insipidus as well as adrenal insufficiency, which is usually secondary adrenal insufficiency (hypothalamic/pituitary). This is because cortisol is required to excrete a water load. These children with adrenal insufficiency and diabetes insipidus who are treated with D-amino D-arginine vasopressin (DDAVP) administration are at risk of water intoxication should they not receive extra doses of hydrocortisone peri-operatively, with ensuing inadequate concentrations of cortisol. Strict fluid balance with adequate cortisol replacement is mandatory to avoid hyponatraemia, which may otherwise be associated with significant morbidity.

Acknowledgements

No conflicts of interest and no competing interests declared. The Guidelines Committee wishes to acknowledge Sonya Daniel, who sourced the Coronial Reports that mandated the development of these guidelines.

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Table 1 Recommended doses for intra- and postoperative steroid cover in adults with primary and secondary adrenal insufficiency

	Intra-operative steroid replacement	**Postoperative steroid replacement**
Surgery under anaesthesia (general or regional), including joint reduction, endoscopy, IVF egg extraction	Hydrocortisone 100 mg intravenously on induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1}	Hydrocortisone 200 mg.24 h^{-1} by intravenous infusion while nil by mouth or for patients with postoperative vomiting Resume enteral – double hydrocortisone doses for 48 h or more. *With rapid recovery* Resume enteral – double hydrocortisone doses for 24 h
Bowel procedures requiring laxatives/enema.	Bowel prep under clinical supervision. Consider intravenous fluids and injected glucocorticoid during preparation, especially for fludrocortisone or vasopressin-dependent patients. Hydrocortisone 100 mg intravenously or intramuscularly at the start of procedure	Resume enteral – double hydrocortisone doses for 24h

Labour and vaginal delivery	Hydrocortisone 100 mg intravenously at onset of labour, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternatively, hydrocortisone 100mg intramuscularly followed by 50mg every 6 hours intramuscularly	Resume enteral – double hydrocortisone doses for 48 h
Caesarean section	See surgery under anaesthesia	

Table 2 Recommended doses for intra- and postoperative steroid cover in adults receiving adrenosuppresive doses of steroids (prednisolone equivalent ≥5mg for 4 weeks or longer)

	Intra-operative steroid replacement	P**ostoperative steroid replacement**
Major surgery	Hydrocortisone 100 mg intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone at 200 mg.24h^{-1}; Alternatively, dexamethasone 6—8 mg intravenously, if used, will suffice for 24h	Hydrocortisone 100 mg.24 h^{-1} by intravenous infusion while nil by mouth. Resume enteral glucocorticoid at pre-surgical therapeutic dose if recovery is uncomplicated. Otherwise continue double oral dose for 48 h
Body surface and intermediate surgery	Hydrocortisone 100 mg, intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternatively, dexamethasone 6—8 mg intravenously, if used, will suffice for 24h	Double regular glucocorticoid dose for 48 hours, then continue usual treatment dose

Bowel procedures requiring laxatives/enema	Continue normal glucocorticoid dose. Equivalent intravenous dose if prolonged nil by mouth
Labour and vaginal delivery	Hydrocortisone 100 mg intravenously at onset of labour, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternatively, hydrocortisone 100mg intramuscularly followed by 50mg every 6 h intramuscularly
Caesarean section	See major surgery

Table 3 Recommended doses for intra- and post-operative steroid cover in children with adrenal insufficiency

Children	**Intra-operative steroid replacement**	**Postoperative steroid replacement**
Major surgery under anaesthesia (general or regional)	Hydrocortisone 2 mg.kg^{-1} at induction followed by immediate continuous intravenous infusion based on weight: Up to 10 kg; 25 mg.24 h^{-1} 11–20 kg; 50 mg.24 h^{-1} over 20 kg; - prepubertal 100 mg.24h^{-1} - pubertal 150 mg.24h^{-1}.	Hydrocortisone 2 mg.kg^{-1} four hourly intravenously or intramuscularly *Or* continuous intravenous infusion based on weight: Up to 10 kg; 25 mg.24 h^{-1} 11–20 kg; 50 mg.24 h^{-1} over 20 kg; - prepubertal 100 mg.24h^{-1} - pubertal 150 mg.24h^{-1}. Once stable, should receive double usual oral doses of hydrocortisone for 48 h and then reduce to normal doses. Add in fludrocortisone if appropriate when enteral feeding established

Minor procedures requiring general anaesthesia	Hydrocortisone 1 $mg.kg^{-1}$ intravenously or intramuscularly at induction of anaesthesia	Double normal hydrocortisone doses once enteral feeding established, and continue on double doses for 24 hours. Add in fludrocortisone if appropriate when enteral feeding established
Minor procedure NOT requiring general anaesthesia	Double morning dose of hydrocortisone given pre-operatively	Normal dose of hydrocortisone