

# Guidelines

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



Association  
of Anaesthetists

February 2020



## Guidelines

# Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency

Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK

**T. Woodcock,<sup>1</sup> P. Barker,<sup>2</sup> S. Daniel,<sup>3</sup> S. Fletcher,<sup>4</sup> J. A. H. Wass,<sup>5</sup> J. W. Tomlinson,<sup>6</sup> U. Misra,<sup>7</sup> M. Dattani,<sup>8,9</sup> W. Arlt<sup>10</sup> and A. Vercueil<sup>11</sup>**

1 Independent Consultant, Hampshire, UK, and Co-chair, Working Party on behalf of the Association of Anaesthetists

2 Consultant, Department of Anaesthesia, Norfolk and Norwich University Hospital NHS Trust, UK

3 Consultant, Adult Intensive Care Unit, University Hospital of Wales, Cardiff, Wales

4 Consultant, Department of Anaesthesia, Norfolk and Norwich University Hospital NHS Trust, UK, on behalf of the Royal College of Anaesthetists

5 Professor, Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK, and Chair, Clinical Reference Group for Endocrinology, on behalf of the Royal College of Physicians

6 Professor, Oxford Centre for Diabetes, Endocrinology and Metabolism, NIHR Oxford Biomedical Research Centre, University of Oxford, Churchill Hospital, Oxford, UK

7 Consultant, Department of Anaesthesia, Sunderland Royal Hospital, Sunderland, UK

8 Professor, Genetics and Genomic Medicine Programme, UCL Great Ormond Street Institute of Child Health, London, UK

9 Consultant Paediatric Endocrinologist and Head of Clinical Service in Endocrinology, Great Ormond Street Hospital for Children, London, UK

10 William Withering Chair of Medicine and Director, Institute of Metabolism and Systems Research, University of Birmingham & Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK, on behalf of the Society for Endocrinology

11 Consultant, Department of Intensive Care Medicine, King's College Hospital, London, UK, and Co-chair, Working Party on behalf of the Association of Anaesthetists

## Summary

These guidelines aim to ensure that patients with adrenal insufficiency are 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 10–15 mg.m<sup>-2</sup> hydrocortisone equivalent or greater in children may result in hypothalamo-pituitary-adrenal axis suppression if administered for 1 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 following surgical stress or illness 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.

Correspondence to: A. Vercueil

Email: editor-vercueil@anaesthetists.org

Accepted: 26 November 2019

Keywords: adrenal insufficiency; glucocorticoids; guidelines; peri-operative medicine; surgical stress

This is a consensus document produced by members of a Working Party established by the Association of Anaesthetists of Great Britain and Ireland, 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 Board of Directors of the Association of Anaesthetists, the Council of the RCoA, and the RCP Executive. It has been endorsed by the British Society for Paediatric Endocrinology and Diabetes and the Society for Endocrinology.

## Recommendations

- 1 Prescribed glucocorticoid therapy (prednisolone  $\geq 5$  mg per day in adults or hydrocortisone-equivalent dose of 10–15 mg.m<sup>-2</sup> per day in children) 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.
- 2 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.
- 3 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 postoperative patients.
- 4 Hydrocortisone 100 mg by intravenous (i.v.) 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.24 h<sup>-1</sup>, 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 back to the appropriate maintenance dose, in most cases within 48 h, although for up to a week if surgery is more major/complicated-clinical judgement should be used to guide this. Intramuscular (i.m.) administration may be prescribed in circumstances where i.v. infusion therapy is impractical (See Tables 1–3 for details).
- 5 Major complications and critical illness excite a prolonged stress response. Any glucocorticoid supplementation should reflect this pattern.
- 6 Dexamethasone is not adequate as glucocorticoid treatment in patients with primary adrenal insufficiency as it has no mineralocorticoid activity.
- 7 Children with adrenal insufficiency are more vulnerable to problems with glycaemic control than adults and require frequent blood glucose monitoring. They can be treated with a bolus of hydrocortisone at induction of anaesthesia followed by an immediate continuous infusion of hydrocortisone, or alternatively with a bolus at induction followed by subsequent four hourly i.v. 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 minimised and adrenal insufficient patients should be prioritised on routine surgical operating lists.

- 8** 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 (20th week onwards), and stress dose supplementation using hydrocortisone 100 mg at the onset of labour, and then either by continuous i.v. infusion of hydrocortisone 200 mg.24 h<sup>-1</sup> or 50 mg intramuscularly every 6 h until after delivery.

### 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 detailed management guidelines for adrenal crisis (<https://www.endocrinology.org/clinical-practice/clinical-guidelines/adrenal-crisis>), and also available in print [5]. In 2016, the Endocrine Society USA released a clinical guideline, focusing on primary adrenal insufficiency [6], with detailed recommendations on stress dosing in the adult patient and the paediatric setting.

### Why was this guideline developed?

In 2012, the Association of Anaesthetists (Association), 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, expressing concern about standards of care for patients with adrenal insufficiency

undergoing surgery. Professors Wass and Artl responded on behalf of the Royal College of Physicians with an editorial in the British Medical Journal [7]. The Association and the Royal College of Anaesthetists welcomed the opportunity to work with the Addison's Clinical Advisory Panel to deliver this updated National Consensus 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 service delivery, and addresses the needs of adults and children.

### Introduction

Patients with a long-standing diagnosis of adrenal insufficiency are often well informed about their disease and may be more knowledgeable 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<sup>-1</sup> at 0900, but only 80–350 nmol.l<sup>-1</sup> at midnight [8]. Cortisol production and release is controlled by adrenocorticotrophic 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].

**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 <sup>-1</sup>	Hydrocortisone 200 mg.24 h <sup>-1</sup> by i.v. infusion while nil by mouth or for patients with postoperative vomiting (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral – double hydrocortisone doses for 48 h or for up to a week following major surgery.  With rapid recovery Resume enteral – double hydrocortisone doses for 24 h
Bowel procedures requiring laxatives/enema.	Bowel prep under clinical supervision. Consider i.v. 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 24 h
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 <sup>-1</sup> Alternatively, hydrocortisone 100 mg intramuscularly followed by 50 mg every 6 h intramuscularly	Resume enteral – double hydrocortisone doses for 48 h
Caesarean section	See surgery under anaesthesia	

i.m., intramuscular; i.v., intravenous.

**Table 2** Recommended doses for intra- and postoperative steroid cover in adults receiving adenosuppressive doses of steroids (prednisolone equivalent  $\geq 5$  mg for 4 weeks or longer).

	Intra-operative steroid replacement	Postoperative steroid replacement
Major surgery	Hydrocortisone 100 mg intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone at 200 mg.24 h <sup>-1</sup> ; Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Hydrocortisone 100 mg.24 h <sup>-1</sup> by i.v. infusion while nil by mouth (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral glucocorticoid at pre-surgical therapeutic dose if recovery is uncomplicated. Otherwise continue double oral dose for up to a week
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 <sup>-1</sup> Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Double regular glucocorticoid dose for 48 h, then continue usual treatment dose if uncomplicated
Bowel procedures requiring laxatives/enema	Continue normal glucocorticoid dose. Equivalent i.v. dose if prolonged nil by mouth Treat as per primary adrenal insufficiency if concerned about hypothalamo-pituitary-adrenal axis function, and risk of adrenal insufficiency	
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 <sup>-1</sup> Alternatively, hydrocortisone 100 mg intramuscularly followed by 50 mg every 6 h intramuscularly	
Caesarean section	See major surgery	

i.m., intramuscular; i.v., intravenous.

**Table 3** Recommended doses for intra- and postoperative 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 <sup>-1</sup> at induction followed by immediate continuous i.v. infusion based on weight: Up to 10 kg; 25 mg.24 h <sup>-1</sup> 11–20 kg; 50 mg.24 h <sup>-1</sup> over 20 kg; - prepubertal 100 mg.24 h <sup>-1</sup> - pubertal 150 mg.24 h <sup>-1</sup>	Hydrocortisone 2 mg.kg <sup>-1</sup> four hourly intravenously or intramuscularly Or continuous i.v. infusion based on weight: Up to 10 kg; 25 mg.24 h <sup>-1</sup> 11–20 kg; 50 mg.24 h <sup>-1</sup> over 20 kg; - prepubertal 100 mg.24 h <sup>-1</sup> - pubertal 150 mg.24 h <sup>-1</sup> . Once stable, should receive double usual oral doses of hydrocortisone for 48 h and then reduce to normal doses over up to a week. Add in fludrocortisone if appropriate when enteral feeding established
Minor procedures requiring general anaesthesia	Hydrocortisone 2 mg.kg <sup>-1</sup> intravenously or intramuscularly at induction of anaesthesia	Double normal hydrocortisone doses once enteral feeding established, and continue on double doses for 24 h. Add in fludrocortisone if appropriate when enteral feeding is established
Minor procedure NOT requiring general anaesthesia	Double morning dose of hydrocortisone given pre-operatively	Normal dose of hydrocortisone

i.v., intravenous.

## 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 (auto-immune adrenal insufficiency) and congenital adrenal hyperplasia. Patients will frequently be deficient in the production of 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; and 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 although it has been claimed not to endanger the functioning of the hypothalamo–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 and inflammatory conditions such as juvenile chronic arthritis and inflammatory bowel disease, and Duchenne's muscular dystrophy accounts for a significant proportion of cases. A Canadian study suggested an incidence of 0.35/100,000 [18]. Primary adrenal insufficiency affects 1 in 8–10,000 children, with congenital adrenal hyperplasia being the most common cause and occurring in 1 in 15,000 live births. Secondary adrenal insufficiency due to ACTH deficiency affects approximately 1 in 10,000 children and can be due to 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 [21–23]. 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.24 h<sup>-1</sup>. If recovery is uncomplicated, we recommend doubling the regular oral replacement dose of hydrocortisone for 48 h, and for up to a week following major surgery 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 postoperatively, 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  $\geq 5$  mg, for longer than 1 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 stresses 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 et al. 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 mg and 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]. Although a precise dose-response relationship could not be demonstrated, these data serve to highlight that a 5 mg dose of prednisolone (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 i.m. injection or i.v. infusion. Recent experiments have established the superiority of i.v. 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 i.v. 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 which 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 antidiuretic 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 in 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:

- 1 Patient reports of non-specific malaise; somnolence or obtunded conscious level; and cognitive dysfunction. The response to 100 mg of hydrocortisone may be tested.
- 2 Monitoring of vital signs should include sitting (or standing) and supine blood pressure, for early detection of orthostatic hypotension.
- 3 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.



- 4 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 effects 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 needs 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 intramuscularly or intravenously in situations of 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 postoperative 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, before 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 h stay' protocol, where available. Ensure that 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, 33–37]. The recommendations for peri- and postoperative surgical stress doses are the same in pregnancy as for other adults. During delivery, 100 mg hydrocortisone should be injected at the onset of active labour (contractions every 5 min for the last hour, or cervical dilation > 4 cm), followed by either continuous infusion of hydrocortisone 200 mg.24 h<sup>-1</sup>, or hydrocortisone 50 mg intramuscularly every 6 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 4 h. No child with adrenal insufficiency should be

fasted for more than 6 h. 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 >10–15 mg.m<sup>-2</sup> per day) [38], should receive an i.v. dose of hydrocortisone at induction (2 mg.kg<sup>-1</sup> for minor or major surgery under general anaesthesia). Postoperatively, 2 mg.kg<sup>-1</sup> hydrocortisone should be administered every 4 h, by the i.v. or i.m. 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 h, 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 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

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. The Guidelines Committee wishes to acknowledge S. Daniel, who sourced the Coronial Reports that mandated the development of these guidelines. No other external funding or competing interests declared.

## References

1. Addison's Disease Self-Help Group. Surgical guidelines for Addison's Disease and other forms of adrenal insufficiency, 2005. <https://www.addisons.org.uk/comms/publications/surgicalguidelines-colour.pdf> (accessed 08/06/2015).
2. Yong SL, Coulthard P, Wrzosek A. Supplemental perioperative steroids for surgical patients with adrenal insufficiency. *Cochrane Database of Systematic Reviews* 2013; **10**: CD005367.
3. Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. *Journal of Internal Medicine* 2014; **275**: 104–15.
4. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes and Endocrinology* 2015; **3**: 216–26.
5. Arlt W, The Society for Endocrinology Clinical Committee. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adults. *Endocrine Connections* 2016; **5**: G1–3.
6. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency. An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2016; **101**: 364–89.
7. Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. *British Medical Journal* 2012; **345**: e6333.
8. Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. *British Journal of Anaesthesia* 2013; **111**: 347–60.
9. Maciejczyk-Pencuła M, Polak G, Kotarski J. Serum cortisol and acute phase protein concentrations after hysterectomy with and without perineal sutures. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2004; **113**: 240–4.
10. Prete A, Yan Q, Al-Tarrach K, et al. The cortisol stress response induced by surgery: A systematic review and meta-analysis. *Clinical Endocrinology* 2018; **89**: 554–67.
11. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *New England Journal of Medicine* 2013; **368**: 1477–88.
12. Gudbjornsson B, Juliusson UL, Gudjonsson FV. Prevalence of long-term steroid treatment and the frequency of decision making to prevent steroid induced osteoporosis in daily clinical practice. *Annals of Rheumatic Diseases* 2002; **61**: 32–6.
13. Levin E, Gupta R, Butler D, Chiang C, Koo JY. Topical steroid risk analysis: differentiating between physiologic and pathologic adrenal suppression. *Journal of Dermatological Treatment* 2014; **25**: 501–6.
14. Levin OS, Polunina AG, Demyanova MA, Isaev FV. Steroid myopathy in patients with chronic respiratory diseases. *Journal of Neurological Sciences* 2014; **338**: 96–101.
15. Chrousos GP, Harris AG. Hypothalamic-pituitary-adrenal axis suppression and inhaled corticosteroid therapy. 1. General principles. *NeuroImmunoModulation* 1998; **5**: 277–87.
16. Chrousos GP, Harris AG. Hypothalamic-pituitary-adrenal axis suppression and inhaled corticosteroid therapy. 2. Review of the literature. *NeuroImmunoModulation* 1998; **5**: 288–308.
17. 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. *European Journal of Endocrinology* 2015; **173**: 663–42.
18. Goldbloom EB, Mokashi A, Cummings EA, et al. Symptomatic adrenal suppression amongst children in Canada. *Archives of Disease in Childhood* 2017; **102**: 338–9.
19. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's

- disease: a population-based study. *Journal of Clinical Endocrinology and Metabolism* 2006; **91**: 4849–53.
20. White K, Wass J. Steroid-dependent patients with multiple comorbidities are more vulnerable to adrenal crisis. *Endocrine Abstracts* 2015; **38**: 416.
  21. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *Journal of Clinical Endocrinology and Metabolism* 2015; **100**: 407–16.
  22. White K, Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *European Journal of Endocrinology* 2010; **162**: 115–20.
  23. Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *European Journal of Endocrinology* 2010; **162**: 597–602.
  24. Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation. *Anaesthesia* 1998; **53**: 1091–104.
  25. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Archives of Surgery* 2008; **143**: 1222–6.
  26. Taylor A, Karavitaki N, Smith D, et al. Prevention of adrenal crisis in stress (The PACS Study): serum cortisol during elective surgery, acute trauma and sepsis in comparison to 'stress dose' hydrocortisone administration in adrenal insufficiency. *Endocrine Abstracts* 2015; **37**: 05.
  27. D'Silva C, Watson C, Ngaage D. A strategy for management of intraoperative Addisonian crisis during coronary artery bypass grafting. *Interactive Cardiovascular and Thoracic Surgery* 2012; **14**: 481–2.
  28. Fraser R, Watt I, Gray CE, Ledingham IM, Lever AF. The effect of etomidate on adrenocortical function in dogs before and during hemorrhagic shock. *Endocrinology* 1984; **115**: 2266–70.
  29. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. *Journal of Trauma* 2008; **65**: 573–9.
  30. Allolio B, Dörr H, Stuttmann R, et al. Effect of a single bolus of etomidate upon eight major corticosteroid hormones and plasma ACTH. *Clinical Endocrinology* 1985; **22**: 281–6.
  31. Allolio B, Stuttmann R, Fischer H, Leonhard W, Winkelmann W. Long-term etomidate and adrenocortical suppression. *Lancet* 1983; **10**: 626.
  32. Quinkler M, Beuschlein F, Hahner S, Meyer G, Schöfl C, Stalla GK. Adrenal cortical insufficiency – life threatening illness with multiple etiologies. *Deutsche Aertzblatt International* 2013; **110**: 882–8.
  33. Royal College of Anaesthetists. Perioperative medicine: the pathway to better surgical care. 2015. <http://www.rcoa.ac.uk/perioperativemedicine> (accessed 08/06/2015).
  34. Albert E, Dalaker K, Jorde R, Berge LN. Addison's disease and pregnancy. *Acta Obstetrica Gynecologica Scandinavica*. 1989; **68**: 185–7.
  35. Nelson-Piercy C. *Handbook of obstetric medicine*. 5th edn. Boca Raton, FL: CRC Press.
  36. Quinkler M, Hahner S, Johansson G, Stewart PM. Saving the lives of patients with adrenal insufficiency; a pan-European initiative? *Clinical Endocrinology* 2014; **80**: 319–21.
  37. Lebbe M, Arlt W. What is the best diagnostic and therapeutic management strategy for an Addison patient during pregnancy? *Clinical Endocrinology* 2013; **78**: 497–502.
  38. British Medical Association, Royal Pharmaceutical Society, the Royal College of Paediatrics and Child Health, and the Neonatal and Paediatric Pharmacists Group. British National formulary for children. 2018-19. <https://www.medicinescomplete.com/#/content/bnfc/PHP107864?hspl=body> (accessed 29/03/2019).



## Safer, for everyone

Every anaesthetist aims to keep their patients safe. We aim to safeguard every anaesthetist – by educating, supporting and inspiring them throughout their career.

**We represent** the life-changing, life-saving profession of anaesthesia – by supporting, informing and inspiring a worldwide community of over 11,000 members.

**Our work and members** span the globe, yet our voice is local and personal. We stay in close contact with our members, look after their day-to-day wellbeing, and act as their champion.

**Our world-class conferences**, journal and online resources educate and inform, and our respected guidelines continually improve standards of patient safety.

**We preserve and learn** from the history of anaesthesia. We use that to inform the present, and facilitate vital research and innovation into its future.

**As an independent organisation**, we speak up freely and openly for the interests of anaesthetists and their patients. We influence policy, raise public awareness and are at the forefront of safer anaesthesia across the world.

Published by  
Association of Anaesthetists  
21 Portland Place, London, W1B 1PY  
Telephone 020 7631 1650 Fax 020 7631 4352  
info@anaesthetists.org  
www.anaesthetists.org

Association of Anaesthetists is the brand name used to refer to both the Association of Anaesthetists of Great Britain & Ireland and its related charity, AAGBI Foundation (England & Wales no. 293575 and in Scotland no. SC040697).



Association  
of Anaesthetists