Emergency and peri-operative management of adrenal insufficiency in children and young people: BSPED consensus guidance

Developed by the Paediatric Adrenal Insufficiency Group on behalf of the British Society of Paediatric Endocrinology & Diabetes (BSPED).

Address for Correspondence:

Dr Talat Mushtaq
Consultant in Paediatric Endocrinology
Old Main Site, Brotherton Wing
Leeds General Infirmary
Leeds, LS1 3EX
Tel: 0113 3926037
Email address: Talat.Mushtaq@nhs.net

Authors and Affiliations

Surname	First (other initial)	Department	Address	email
Mushtaq	**Talat**	Department of paediatric endocrinology	Leeds Children's Hospital, UK	Talat.mushtaq@nhs.net
Ali	Salma R	Developmental Endocrinology Research Group	Royal Hospital for Children, University of Glasgow, Glasgow G51 4TF, UK	salma.ali@glasgow.ac.uk
Boulos	**Nabil**	Pharmacy Department	Southampton University Hospitals NHS Foundation Trust, Southampton, UK	nabil.boulos@uhs.nhs.uk
Boyle	**Roisin**	Department of paediatric endocrinology	Royal Hospital for Children, Glasgow G51 4TF, UK	Roisin.Boyle@ggc.scot.nhs.uk
Cheetham	**Tim**	Department of paediatric endocrinology	Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, UK	tim.cheetham@nhs.net
Davies	**Justin H**	Department of Paediatric Endocrinology	Southampton University Hospitals NHS Foundation Trust, Southampton, UK	Justin.Davies@uhs.nhs.uk
Elder	**Charlotte J**	Department of Endocrinology	Sheffield Children's NHS Foundation Trust, Sheffield, United Kingdom	c.j.elder@sheffield.ac.uk
Gan	**Hoong-Wei**	Department of Paediatric Endocrinology	Great Ormond Street Hospital for Children, London, UK	hoong.gan.11@ucl.ac.uk
Hindmarsh	Peter C	Developmental Endocrinology Research Group	University College London Hospitals, London NW1 2BU, UK	p.hindmarsh@ucl.ac.uk
Katugampola	Harshini	Department of Paediatric Endocrinology	Great Ormond Street Hospital for Children, London, UK	Harshini.Katugampola@gosh.nhs.uk
Krone	Nils P	Department of Oncology and Metabolism	University of Sheffield Beech Hill Rd Sheffield S10 2RX	n.krone@sheffield.ac.uk
SalomonEstebanez	Maria	Department of Paediatric Endocrinology	Royal Manchester Children's Hospital, Manchester, UK	Maria.SalomonEstebanez@mft.nhs.uk
Shenoy	Savitha	Department of Paediatric Endocrinology	University Hospitals Of Leicester NHS Trust, Leicester, UK	savitha.shenoy@uhl-tr.nhs.uk
Tollerfield	**Sally**	Department of Paediatric Endocrinology	Great Ormond Street Hospital for Children, London, UK	Sally.Tollerfield@gosh.nhs.uk
Wong	**Sze Choong**	Department of Paediatric Endocrinology	Royal Hospital for Children, University of Glasgow, Glasgow G51 4TF, UK	Jarod.Wong@glasgow.ac.uk
Regan	**Fiona**	Department of Paediatric Endocrinology	Guy's and St Thomas' NHS Foundation Trust, London, UK	Fiona.Regan@gstt.nhs.uk

Abstract

Adrenal insufficiency (AI) is characterised by lack of cortisol production from the adrenal glands. This can be a primary adrenal disorder or secondary to adrenocorticotropic hormone (ACTH) deficiency or suppression from exogenous glucocorticoids. Symptoms of AI in children may initially be non-specific and include growth faltering, lethargy, poor feeding, weight loss, abdominal pains, vomiting and lingering illnesses. AI is treated with replacement doses of hydrocortisone. At times of physiological stress such as illness, trauma or surgery there is an increased requirement for exogenous glucocorticoids, which if untreated can lead to an adrenal crisis and death. Currently, there are no unified guidelines for those <18 years old in the UK; this can lead to a substantial variation in the management of AI in emergency and peri-operative situations. This paper sets out guidance for intercurrent illness, medical, dental and surgical procedures to allow timely and appropriate recognition and treatment of AI and adrenal crisis (AC).

Background

Most forms of adrenal insufficiency (AI) are characterised by lack of cortisol production from the adrenal glands. Children with AI have a daily requirement for glucocorticoid at a replacement dose, but at times of physiological stress require additional exogenous glucocorticoids, usually given as hydrocortisone. Clinical features at presentation can vary with age and the dose required for a neonate with AI will be different to that of a teenager. The diagnosis of AI in children is often delayed because symptoms can be non-specific and overlap with other common childhood conditions. Failure to recognise and instigate prompt treatment of AI can result in life-threatening adrenal crises. There are three scenarios that require bespoke management: adrenal crisis (AC), sick day episodes and peri-operative management.

The emergency management and peri-operative care of childhood (0-18 years) AI is different to that required in adults in that treatment requires a nuanced approach, based on age, weight or surface area. Moreover, the management of primary AI is necessarily different to that of secondary AI especially in relation to fluid management. Failure to recognise these different management strategies can lead to severe iatrogenic complications. In August 2020, there was a national patient safety alert to support early recognition and treatment of an adrenal crisis in adults highlighting that untreated AI can be fatal. Guidelines for emergency management of adults (over 18 years) with AI have recently been published (Simpson et al 2020).

Currently, there are no unified guidelines for patients younger than 18 years in the UK. This can lead to a substantial variation in the management of AI in both an emergency and peri-operative situation. This results in the potential for over- and under treatment and causes a lack of consistency when providing education and training to families and health professionals.

In 2021 the Paediatric Adrenal Insufficiency Group was set up under the auspices of the British Society of Paediatric Endocrinology & Diabetes (BSPED) in an effort to standardise the management of paediatric AI across the UK. The group consisted of 16 individuals from 11 UK tertiary endocrine units and included paediatric endocrinologists, specialist nurses and a paediatric pharmacist. This is a consensus document of the BSPED PAIG and incorporated the views of other stakeholders including clinicians and patient organisations.

Causes of AI

Primary AI occurs due to pathologies of the adrenal glands (such as autoimmune Addison's disease or congenital adrenal hyperplasia) and is usually associated with both glucocorticoid and mineralocorticoid deficiency. There may also be evidence of hyperpigmentation in primary AI. Secondary AI is due to pathologies of the pituitary gland where a lack of ACTH leads to cortisol deficiency (e.g. hypopituitarism). Suppression of ACTH leading to AI may also be due to exogenous high dose glucocorticoid use (tertiary AI). Symptoms of AI may initially be non-specific and include growth faltering, lethargy, poor feeding, abdominal pains, vomiting, weight loss and lingering illnesses. Infants may develop hypoglycaemia irrespective of the cause of AI. A recent review provides a comprehensive summary of causes of AI in children in adults (Husebye ES 2021).

Definition of an adrenal crisis

An acute adrenal crisis (AC) is a life-threatening deterioration due to glucocorticoid insufficiency which may result in cardiovascular instability, abnormalities of plasma electrolytes, seizures and death. Definitions of an adrenal crisis in adults include an acute deterioration in health status associated with absolute hypotension; the features of which resolve within 1 to 2 hours of parenteral glucocorticoid treatment.

Identification of hypotension in children is more difficult and thus adult definitions of adrenal crisis cannot be easily transferred to the paediatric population. Therefore the comprehensive review in 2018 (Rushwoth et al) proposes an updated definition of AC in children which also includes improvement of symptoms following glucocorticoid administration (Table 1)

The main risk factors for AC are younger age at diagnosis, primary AI, mineralocorticoid treatment and recurrent hospital admissions (Eyal O, 2019). Children with diarrhoea and vomiting illness are at particular risk of adrenal crisis, which may be refractory to standard stress dosing, due to lack of absorption of their glucocorticoid treatment (Rezai et al 2022). Other risk factors include new onset seizures, trauma and, fractures. At presentation, children may have non-specific symptoms including pyrexia, abdominal pain, nausea and vomiting (Worth et al 2021).

Incidence of adrenal crisis

Most estimates of AC are derived from adult populations where approximately one in 12 patients will experience a life-threatening crisis within the next 12 months and one in 200 adult patients with AI will die from an adrenal crisis (Allolio, EJE 2015). In children the literature is limited. A national paediatric surveillance program in Canada reported 46 cases of AI, of which 6 (13%) had had an adrenal crisis (Goldbloom et al, 2017). Recent studies evaluating the occurrence of adrenal crises in children with Congenital Adrenal Hyperplasia (CAH) have reported variable rates of 6.5 to 10.9 adrenal crises per 100 patient years and a threefold increase in standardised mortality rate particularly in the 1-4 years age group (Ali. JCEM 2021, Odenwald. 2016, Swerdlow. Peds 1998). However, these estimates may not be transferrable to all forms of AI in childhood. A single centre UK study estimated an incidence of 1 death per 300 patient years in their cohort (Worth et al 2021).

Paediatric patients who should be considered to be at risk of adrenal crisis:

Glucocorticoids are utilised for multiple different indications and administration by any route can cause AI, however dose, duration and potency, though important, are imperfect predictors of AI. Defining the paediatric patients at risk of adrenal crisis is outside the scope of this guidance. There is published guidance for adults (Simpson et al 2020), children (BNFc and Neonatal and Paediatric Pharmacy Group (NPPG (NPPG)), and for those prescribed inhaled corticosteroids (BTS/SIGN/NICE). The NPGG guidance covers doses of glucocorticoids and their respective routes of administration and recommends when a steroid treatment card stating the child is *at risk of AI* should be issued. This should be the responsibility of the prescribing clinician (NHSE Safety alert). Those children with *confirmed AI* should be provided with the BSPED AI leaflet (updated 2022) and a plan for sick day glucocorticoids along with training in how to administer emergency hydrocortisone injections.

Methods

In 2020, the BSPED clinical committee agreed the need for standardised guidance on the management of AI in children with a focus on the management during acute illness including oral sick day dosing, intramuscular (IM) and intravenous (IV) regimens during emergencies, inpatient management and during the peri-operative period. Applications for the paediatric AI working group were advertised in the BSPED newsletter and a group of 16 professionals, from ten tertiary centres, was convened in March 2021 (12 paediatric endocrinologists, 1 paediatric endocrinology trainee, 2 paediatric nurses, 1 paediatric pharmacist). An initial literature search was performed and these, along with existing UK hospital guidelines for management of paediatric AI, were circulated to members of the BSPED paediatric AI working group. The working group was divided into two sub-groups with one subgroup focussing on management of oral sick day episodes and the other on management requiring IM and/or IV treatment. Sub-group recommendations were distributed to the whole working group to obtain consensus. The final draft consensus was circulated to relevant stakeholders including the BPSED clinical and executive committees, the BSPED membership, Society for Endocrinology clinical committee and patient organisations including the CAH support group, Addison's Disease Self-Help Group and The Pituitary Foundation.

Current management and issues

Currently there are different management strategies for different scenarios utilised by centres across the UK. Infants and children are typically provided with age based doses for intramuscular hydrocortisone (typically 25mg < 1year, 50mg 1 to 5 years and 100mg 6 years and older). The same doses are often used at induction for surgery and then at six hourly intervals if required. Some units utilise hydrocortisone infusions as first line management during surgery. The current bolus doses of 100mg in those over 6 years given every six hours are likely to lead to overexposure of glucocorticoids and are hard to justify in light of adult guidance recommending 200mg hydrocortisone in 24 hours (Simpson et al 2020).

During sick day episodes, the required increase in oral glucocorticoid doses may be in the form of doubling or tripling glucocorticoid doses for mild and moderate illness and giving these three or four times a day. However, definitions for severity of illness are difficult to quantify and practise varies widely on when sick day glucocorticoids are advocated for specific situations (Ali SR et al 2022).

There has been a change in recent years with a number of UK centres advising specific sick day doses based on a body surface area of 30mg/m^2/day given in 4 equally divided doses every 6 hours.

Presently, for the management of AI, there are age and weight-based hydrocortisone doses, as well as doses based on body surface area. Each approach has merits and downsides. Age based doses are easy to remember but will cause significant variations depending on the individual weight and body surface area. Whilst weight based doses are very commonly used in paediatrics, presently there is no suggested maximum recommended daily hydrocortisone dose such as with adult guidance which advocates 200mg a day (Simpson et al, 2020). Body surface area based doses are potentially more accurate, particularly in infants who have a relatively larger body surface area, but are less easy to calculate, in urgent situations. Therefore, a collective effort was made to combine these into a simpler structure, based on doses from published recommendations and those presently in use.

NHS England operates the National Reporting and Learning System (NRLS). Incident level patient safety data on reporting harm occurring in children with AI / AC over a three year period from Sept 2019 to Aug 2022 was obtained. During this period there were 83 reports of individuals who were at risk from issues related to timely treatment and management of AI. Of these, one incident of them was reported as severe harm and two, moderate harm. As these incidents are self-reported events by staff, it is likely that the true number of incidents is higher; however, three common themes emerged from these reports, 1) Glucocorticoids not given around surgery 2) Glucocorticoids not given as prescribed (included delayed or missed doses) and 3) Issues in the community due to combinations of training, recognition or access to treatments for AI from caregivers.

Literature review and published recommendations of hydrocortisone doses

Many recommendations of hydrocortisone doses are based on expert consensus and established practice, with data often extrapolated from adult studies. A recent comprehensive Cochrane review encapsulates the lack of good quality evidence on which to base recommendations for treatment specifically in CAH; in particular there are a limited number of trials comparing efficacy of different glucocorticoid regimens and no trials included long term outcomes such as prevention of adrenal crisis (Ng SM 2020. Cochrane Database).

A common recommendation to manage AI sick days is to increase the oral sick day hydrocortisone to 30 to 50 mg/m^2 per day (at least tripling a daily replacement dose) divided into 3 or 4 doses over the day (Shulman et al 2006).

For an acute adrenal crisis the published recommended doses of hydrocortisone range from 50 to 100 mg/m^2 IV or IM initially, followed by 50 to 75mg/m^2/day or up to 100 mg/m^2 per day either as a continuous infusion or in four divided doses given every 6 hours by IV (or IM) route (Shulman D et al 2006, Rushworth L et al 2019, Nowotny H et al 2021).

For those having surgical procedures, parenteral hydrocortisone is recommended in published literature with a preoperative dose of 50 mg/m^2 around 30 to 60 minutes before induction of anaesthesia. A second dose of 50 mg/m^2 can then be administered as a continuous infusion or as an intravenous bolus divided every 6 hours over the next 24 hours. The most severe stresses, such as

major surgery or sepsis, are often treated more aggressively, with doses up to 100 mg/m^2 per day divided every 6 hours intravenously (Shulman D et al 2006, Rushworth L et al 2019).

Weight based peri-operative recommendations by Woodcock et al advise hydrocortisone doses of 2mg/kg at induction, followed by an infusion or 2mg/kg at 4 hourly intervals without stating a maximum dose (Woodcock et al 2020). The British National Formulary for Children (BNFc) BNFc hydrocortisone) recommends an initial dose of 10mg for neonates in acute AI then 100mg/m^2/day either as an infusion or in divided doses. From one month to 11 years the recommended dose is 2 - 4 mg/kg every 6 hours and from 12 to 17 years it is 100mg every 6 to 8 hours.

The recent UK guidance in adults with AI advises hydrocortisone 100mg IV for acute adrenal crisis or for induction for surgical procedures. This is followed by an infusion of hydrocortisone 200mg in 24 hours or alternatively can be given as 50mg IV every 6 hours. In severe obesity 100mg of hydrocortisone can be substituted for the 50mg dose of hydrocortisone (Simpson et al 2020).

Therefore, a number of principles were considered in the development of this paediatric guidance. These included harmonising the recommended maximum dose of 200mg in 24 hours in adults with older teenagers, and developing recommendations for children that provided doses of 50 to 100mg/m^2/day for surgical procedures and doses of around 30mg/m^2/day for oral sick day hydrocortisone. Neonates require higher weight based doses due to a relatively larger surface area. Oral maintenance doses for glucocorticoids are based on the surface area of the child. Thus, the surface area approach is used for the oral sick day hydrocortisone recommendations for children undergoing regular follow-up in the endocrine clinic. For emergency and peri-operative management, weight based oral sick day hydrocortisone doses are recommended.

BSPED consensus recommendations for oral glucocorticoid dose for sick day episodes:

Children on daily glucocorticoid replacement for AI have hydrocortisone doses calculated for surface area with doses of around 8mg/m^2/day for physiological replacement (Peters CJ et al, 2013) and higher doses around 10 - 15mg/m^2/day to optimise growth in children with CAH. These are administered as 3 or 4 times a day dosing regimens. (Claahsen-van der Grinten HL et al. 2022)

Our preferred recommended option for management of sick day episodes is a dose based strategy aiming for a total daily hydrocortisone dose of around 30mg/m^2/day given as four equally divided doses. This allows accuracy of dosing at regular 6 hourly intervals, avoiding long gaps between doses and overcomes the relatively short half-life of oral hydrocortisone (Hindmarsh & Charmandari 2015). This will ensure that adequate plasma levels are maintained during times of stress. Increased doses should be utilised for the duration of the illness. However, with improvement of the underlying illness the frequency and duration of the hydrocortisone treatment can be adjusted to suit the individual circumstance. The advantages of this approach (compared with a doubling or tripling approach) are that children with AI of any cause will all broadly have the same sick day episode hydrocortisone dose. Therefore, there is no need to discern between those on relatively low doses of physiological glucocorticoid replacement to those on slightly higher doses as used in CAH.

Whilst schedules that include doubling of hydrocortisone for mild illness or tripling for moderate illness and / or recommending an additional early morning dose are all acceptable, the potential

downside with this strategy is that the individual may under dose or over shoot the sick day episode hydrocortisone requirements, which may potentially have deleterious metabolic consequences. Furthermore definitions for mild and moderate illness can be subjective and difficult to quantify objectively.

Supplementary material 1 outlines the common situations when additional sick day episode oral and emergency hydrocortisone is recommended. Supplementary material 2 provides pre-calculated hydrocortisone sick day episode doses for a range weights as a further aid for families and clinicians.

Fludrocortisone (Florinef) is an oral mineralocorticoid used in primary AI. The dose does not need adjustment in the event of a sick day episode or an adrenal crisis. It should be continued as usual. If the child is unable to take oral medication then intravenous fluids may be required to maintain the salt and water balance depending on the clinical situation. However, the mineralocorticoid effect of hydrocortisone at stress doses is often sufficient to cover the mineralocorticoid requirement. Oral fludrocortisone should be re-commenced when tolerated.

BSPED consensus recommendations for oral glucocorticoid dose for sick day episodes: Specific situations

In patients on supra-physiological glucocorticoid therapy such as **prednisolone, deflazacort** or **dexamethasone** for an existing chronic condition, a simple and safe approach is to consider additional hydrocortisone, at sick day doses to ensure adequate plasma cortisol levels throughout the day and night. Alternatively, if the child is taking a glucocorticoid at over 30mg/m^2/day of a hydrocortisone equivalent dose, then further sick day doses with additional hydrocortisone may not be necessary in principle; but they should have a bespoke plan for the management of AI. For those on regular prednisolone, our recommendation is for sick day dosing with hydrocortisone. If this is not practical, then prednisolone 7.5mg/m^2/day given in two divided doses can be utilised. If the existing prednisolone dose is greater than the required sick day dose, then the prescribed prednisolone should be split into two doses given at 12 hourly intervals. The relatively short half-life of deflazacort (1.5 to 1.9 hours) necessitates the use of sick day dosing with hydrocortisone. For patients on enzyme inducing medications higher sick day doses may be required (NPPG).

For patients prescribed **Alkindi**, increase doses as per sick day guidance utilising either Alkindi granules in capsules for opening (if available) or oral hydrocortisone (immediate release preparation).

If the child is on twice daily **Efmody** (modified release hydrocortisone), they should be switched to immediate release oral hydrocortisone as per sick day episode guidance in four divided doses whilst unwell. Alternatively, Efmody may be continued at the usual dose and additional immediate release hydrocortisone added in four divided doses to provide a combined (Efmody and immediate release oral hydrocortisone) glucocorticoid dose of 30mg/m^2/day.

BSPED consensus recommendations for treatment of adrenal crisis:

Management of AC includes urgent administration of glucocorticoids, along with assessment and treatment of hypoglycaemia, hypotension and dehydration and these should be managed as in table

2 (Rubens M & Kanaris C ADC 2021). Young people (16 to 18 years) admitted under the care of adult services should be managed as per the Society For Endocrinology guidelines: https://www.endocrinology.org/adrenal-crisis.

- Glucocorticoids: Hydrocortisone 100mg for injection is available as a premixed solution in a 1ml volume (hydrocortisone sodium phosphate) or reconstituted with a provided vial of 1ml vial of water for injection (hydrocortisone sodium succinate). The first dose is often given in the community setting by the family or attending paramedics. In infants and children it is convenient to advise a dose strength based on a volume of injection that is easy to draw up. Table 2 details the current BSEPD consensus recommendations. Our recommendations for IM hydrocortisone include age based cut-off levels for those less than 1 year age, 1 to 5 years and 6 years and over (Table 2). Thus the average sized infant (3.5 kg to 10kg) less than 1 year old will have doses of 50 to 100mg/m^2/dose. For those aged 1 to 5 years (10 to 20kg / body surface area 0.5 to 0.79mg/m^2), the dose range is from 63 to 100mg/m^2 and for those over 6 years (20kg to 76kg / body surface area 0.79 to 2m^2) the doses are 50mg/m^2 in the older teenagers and 126mg/m^2 for the average weight 6 year old. Consideration was therefore given to providing a higher age cut-off age of 10 years for the maximum dose. However, as around a third of the childhood population are overweight or obese (National Child Measurement Programme 2020/21) a significant proportion of older children (aged 8 or 9 years) may be relatively under dosed if they were recommended a dose of 50mg. Practically it was considered more straightforward to give a full 100mg dose from 6 years of age as a slightly generous one-off emergency dose in a small cohort of children weighing between 20 to 30kg is unlikely to do any harm for an event that is likely to occur infrequently (Table 2).

For children presenting acutely unwell to hospital or any other emergency situation, the same age based hydrocortisone doses as in table 2 can be utilised for initial management given either by the IM or IV route. Alternatively weight based doses can be utilised for immediate care and then for on-going care as in table 2. As premature infants and neonates have a relatively larger surface area an initial dose of 4mg/kg is recommended compared to 2mg/kg for older infants and children.

- Hypoglycaemia: Blood glucose should be checked and hypoglycaemia treated with 2ml/kg of 10% dextrose as an IV bolus (table 2).

- Hyponatraemia and fluids: Sodium chloride 0.9% / 5% dextrose is usually a good starting point for initial fluid management if the clinical and biochemical picture suggest that the low sodium has arisen primarily because of salt wasting. In primary AI insufficiency (eg CAH, Addison's disease), mineralocorticoid deficiency will cause hyponatraemia due to renal losses. In secondary AI (eg congenital hypopituitarism, CNS lesions, adrenal suppression from use of high dose glucocorticoid), cortisol deficiency can lead to a lack of free water clearance which can contribute to hyponatraemia. In this latter scenario (those with secondary AI), a degree of fluid restriction may be more appropriate. There is however no substitute for calculating the sodium deficit and replacing over a suitable time period dictated by duration of illness and initial plasma sodium concentration. Our recommendations on fluid management taking into consideration of the aetiology of AI is listed in Table 2 and supplementary material table 3.

- Hyperkalaemia: Children with primary AI can be hyperkalaemic at presentation or in an AC because of mineralocorticoid deficiency. Emergency management of AC with IV glucocorticoids and IV fluids

(0.9% sodium chloride) will reduce potassium levels. Hyperkalaemia is potentially life-threatening and can lead to cardiac arrhythmias so additional measures such as the use of IV calcium gluconate, nebulised salbutamol, IV insulin and dextrose or IV bicarbonate and cation exchange resins should also be considered (Rubens M & Kanaris C ADC 2021). (Supplementary material table 3).

BSPED consensus recommendation for the management of dental, medical and surgical procedures:

Individuals with AI are unable to mount a stress response during events that cause major physiological stress such as medical or surgical procedures, thus additional hydrocortisone is required. There is a paucity of evidence-based guidelines for management of AI in children having surgical procedures; consequently there are a number of treatment strategies utilising either hydrocortisone infusions or bolus doses. In a study comparing the serum cortisol levels in adult patients without AI undergoing major stress events such as sepsis, trauma and elective surgery to patients with AI who were given different hydrocortisone dose schedules by different routes of administration, the modelling identified a continuous intravenous infusion of 200 mg hydrocortisone over 24 hours, preceded by an initial bolus of 50–100 mg hydrocortisone best matched the cortisol responses in patients without AI experiencing major stress. The recommendation in this paper in adults favoured a continuous intravenous infusion to intermittent bolus regime (Prete A, JCEM 2020). Further guidance in adults recommends a pre-surgery bolus of 100mg followed by 200mg of hydrocortisone either as an infusion over 24 hours or given as 50mg every 6 hours (Simpson et al 2020). Paediatric AI regimens require a dose titration based on weight but it would seem prudent to ensure that older teenagers are managed with similar doses to adults.

Our recommended glucocorticoid doses for major surgery are given in table 3; this includes an initial bolus of hydrocortisone of 2mg/kg in children or 4mg/kg in neonates (less than 28 days corrected gestational age); followed by either a continuous infusion or as intermittent bolus doses. It would seem prudent to use the neonatal dosing for infants who are significantly small for gestational age or failing to thrive and as such, whilst not neonates, are a neonatal size. The overall 24 hour hydrocortisone dose for all groups is thus well within or just above the recommended doses of 50 to 100mg/m^2/day (Rushworth NEJM 2019). A safety net has been built into the guidance to consider continuing the initial higher bolus dose either at 6 hours or to consider 4 hourly dosing for prolonged major surgical procedures or if the patient is unstable. Our recommendations for minor procedures are provided in Table 4. Further details in supplementary material 4 provide a comparison of hydrocortisone bolus doses based on weight and surface area for neonates, children and teenagers and confirms that across all weight ranges they have more than the minimum recommended dose of 50mg/m^2/day.

It should usually be possible for the child to continue with their usual oral glucocorticoid pre-operatively even if fasting. Peri-operatively, all children with AI should be given additional hydrocortisone at induction and during surgery and ideally be first on the operating list. The period of fasting should not be more than 6 hours without IV fluid replacement that includes saline and dextrose. Children are at particular risk of hypoglycaemia and if not on IV saline and dextrose should have regular capillary blood glucose every 2 hours until oral feeds or fluids are commenced.

For elective surgical procedures, assuming the patient is haemodynamically stable and the electrolytes are normal, an assessment needs to be made about the patient's hydration status and IV fluids considered depending on the type and length of procedure. 0.9% saline / 5% dextrose at a maintenance rate is usually appropriate as in table 2. A more detailed fluid assessment is required if IV fluids are necessary for more than 48 hours or in patients with primary AI on fludrocortisone as fludrocortisone cannot be given IV. Thus the lack of mineralocorticoid replacement may result in sodium loss (particularly on replacement hydrocortisone which has less mineralocorticoid effect when compared to sick day doses).

Education, Information Sharing and Discharge planning for children with AI

Every child with confirmed AI requires a comprehensive package of information and education along with a management plan for urgent care as in the table 5. Following diagnosis the clinical team responsible for on-going care should be informed and education initiated as soon as possible to ensure that the child or young person and their family are confident in managing AI on discharge home. The education and confidence with sick day episode treatment should be reiterated during clinical visits. A BSPED AI leaflet (available from the **BSPED AI webpage)** with details of their maintenance and sick day doses of hydrocortisone along with details of clinical team should be provided and periodically reviewed. Hospital records should have an alert in place to indicate that the child has AI (table 5). A checklist is available on the BSPED website for use by medical professionals to record and document that appropriate information, education and training has been provided (**BSPED AI webpage)**

Summary and conclusions

Prompt recognition and treatment of AI is essential to prevent a life-threatening adrenal crisis. Glucocorticoid doses should never be omitted and emergency treatment should not be delayed especially when presenting to acute medical teams. The risks of AI and AC can be reduced by effective patient education, training for medical staff and AI alerts on hospital records. This guidance should serve as a foundation to improve the care and treatment of children with AI.

Acknowledgements

The BSPED Paediatric AI group would like to acknowledge the contributions of the BSPED clinical committee, BSPED executive committee, SFE, CAH support group, Addison's Disease Self-Help Group, Pituitary Foundation. We are also very grateful to the Patient Safety Team at NHS England for providing the incident level patient safety data.

List of tables and supplementary material

Table 1: Definition of an adrenal crisis in paediatric patients (adapted from Rushworth et al 2018)

Definition of an adrenal crisis in paediatric patients	**Additional details**
An acute deterioration in health that is associated with • acute haemodynamic disturbance (hypotension or sinus tachycardia relative to age-related normal levels) • or a marked abnormality in one or more electrolytes (hyponatraemia, hyperkalaemia) • or hypoglycaemia that is not attributable to another illness, the features of which show significant resolution following parenteral glucocorticoid administration	Frequent concomitant features include: • acute abdominal symptoms • altered levels of consciousness/obtundation • nausea/vomiting • poor feeding (in infants) • pyrexia Consideration of the effects of incidental illness as causes of the major features, in particular shock, improves the specificity of diagnosis
Symptomatic AI (Rushworth Endo 2017)	
Unwell but not yet having an adrenal crisis. Often admitted to hospital for treatment of milder symptoms, such as • Postural dizziness • Nausea and abdominal discomfort • Lassitude • Poor feeding in younger patients	May be a precursor to adrenal crisis

Table 2: Emergency Management of Paediatric Adrenal Crisis

British Society of Paediatric Endocrinology & Diabetes Adrenal Insufficiency Guidance: (link)		
Emergency Management of Paediatric Adrenal Crisis in the COMMUNITY		
Intramuscular (IM) hydrocortisone doses or initial IV dose *		
Age	**IM dose of hydrocortisone**	**Indications for hydrocortisone**
Less than 1 year	25mg	• Acutely unwell and unable to get IV access • Acutely unwell with diarrhoea and vomiting and unable to tolerate oral treatment • Reduced responsiveness or loss of consciousness. • Hypoglycaemic or new onset seizure in known or suspected adrenal insufficiency. • Fracture / significant burn
1 to 5 years	50mg	
6 years and over	100mg	
Emergency Management of Paediatric Adrenal Crisis in HOSPITAL		
Children (>28 days) *	**Hydrocortisone dose and frequency**	
Severe illness	1) Age based doses given IM or IV (25mg < 1year, 50mg 1 to 5 years, 100mg for 6 years and over - subsequent doses as in 2) below *or* 2) 2mg/kg (max 100mg) IV bolus initially then bolus dose 6 hourly* (*can consider giving 4 hourly or as an infusion (table 4) if needed)	
Stable and improving	1mg/kg (max 50mg) IV 6 hourly (can consider giving 4 hourly or as an infusion (table 4)	
Stable and tolerating drinks / diet	Oral sick day steroids: 30mg/m^2/day in 4 equally divided doses Restart fludrocortisone if indicated	
Neonates (<28 days)	**Hydrocortisone dose and frequency**	
Severe illness	4mg/kg IV initially 6 hourly (*can consider giving 4 hourly or as an infusion (table 4) if needed)	
Stable and improving	2mg/kg IV 6 hourly (can consider giving 4 hourly or an infusion (table 4)	
Stable and tolerating drinks / diet	Oral sick day steroids: 30mg/m^2/day in 4 equally divided doses Restart fludrocortisone if indicated	
Fluid type and volume		
Blood Glucose < 3mmol/L	2ml/kg of 10% dextrose as IV bolus Recheck blood glucose after 15 minutes and repeat bolus if necessary.	
Shock or moderate to severe dehydration	Give 10ml/kg of 0.9% sodium chloride as a bolus and repeat if necessary Check electrolytes immediately at presentation to inform fluid usage (Table 3)	
Maintenance fluids type and amount	0.9% sodium chloride / 5% dextrose is usually an appropriate starting point: 100ml/kg/day for 1st 10kg, 50ml/kg/day for 2nd 10kg, 20mls/kg/day >20kg	

Treatment should not be delayed. A safe approach is to administer emergency hydrocortisone in any unwell child with AI. The child must be observed until they are tolerating oral hydrocortisone at sick day doses.

*It would seem prudent to use the neonatal dosing for infants who are significantly small for gestational age or failing to thrive and as such, whilst not neonates, are a neonatal size.

Young people (16 to 18 years) admitted under the care of adult services should be managed as per the society of endocrinology guidelines: https://www.endocrinology.org/adrenal-crisis

See supplementary material 3 for more detailed guidance about fluid and electrolyte management in AC and different considerations for primary and secondary AI.

Table 3: Recommended doses for peri and post-operative glucocorticoid cover in children with AI undergoing major surgery utilising either a continuous infusion (3.1) or intermittent bolus in children (3.2a) and neonates (3.2b)

Major Surgery is defined as surgery lasting more than 90 minutes with variable recovery periods and expected delay in restarting oral intake. Management includes an initial bolus of hydrocortisone followed by either a hydrocortisone infusion or regular bolus doses.

British Society of Paediatric Endocrinology & Diabetes Adrenal Insufficiency Guidance: : (link)			
3. MAJOR SURGERY: Hydrocortisone doses for infusion or bolus			
3.1 Major Surgery: Intravenous Infusion (IVI) hydrocortisone doses			
Induction	IV bolus of hydrocortisone 2mg/kg (max 100mg) (premature infants and neonates < 28 days corrected gestational age: 4mg/kg)		
Intraoperative	**IV hydrocortisone infusion as below**		
Weight	**Total dose in 24 hours**	**Infusion rate (50mg hydrocortisone in 50ml 0.9% sodium chloride*)**	**Additional considerations**
≤10kg	25 mg	1 ml/hr	- Consider more concentrated infusion in those needing fluid restriction (e.g. 100mg hydrocortisone in 50mls 0.9% saline). - The hydrocortisone infusion can be run alongside 0.9% sodium chloride, 5% glucose and PlasmaLyte solutions
10.1 to 20kg	50 mg	2 ml/hr	
20.1 to 40kg	100 mg	4 ml/hr	
40.1 to 70kg	150 mg	6 ml/hr	
Over 70kg	200 mg	8 ml/hr	
Post-operative	Continue hydrocortisone infusion Change to oral sick day hydrocortisone when stable and tolerating oral fluids / diet		
3.2 a) Major Surgery: Child (over 28 days corrected gestational age) Intravenous Hydrocortisone Bolus doses			
	Hydrocortisone bolus dose	**Frequency**	**Additional considerations**
Induction	**2mg / kg (max 100mg)**		- Consider neonatal doses (3.2b) for infants who are significantly small for gestational age or with growth faltering
Intraoperative	**2mg / kg (max 100mg)**	Given at 6 hours IV	- Consider infusion for prolonged procedures - 4 hourly if unstable
Post-operative	**1mg / kg (max 50mg)**	Every 6 hours IV Change to oral sick day hydrocortisone when stable and tolerating oral fluids / diet	- In severe obesity consider substituting 50 mg hydrocortisone with 100 mg hydrocortisone
3.2 b) Major Surgery: Premature infants and neonates (less than 28 days corrected gestational age) Intravenous Hydrocortisone Bolus doses			
	Hydrocortisone bolus dose	**Frequency**	**Additional considerations**
Induction	**4mg / kg**		
Intraoperative	**2mg / kg**	Given at 6 hours IV	- Consider infusion for prolonged procedures - 4mg/kg if unstable or consider 4 hourly doses
Post-operative	**2mg / kg**	Every 6 hours IV Change to oral sick day steroids when stable and tolerating oral feeds	- The oral dose can be given IV if not tolerating feeds

Table 4: Recommended glucocorticoid cover in children with AI undergoing minor procedures requiring (4.1) or not requiring (4.2) a general anaesthetic

4.1 Minor procedures requiring general anaesthesia

Minor Surgery is defined as a procedure lasting less than 90 minutes and the patient is expected to be eating and drinking by the next meal. This may include procedures such as MRI scans, endoscopy, dental extractions under general anaesthetic or other day case procedures. If the procedure exceeds four hours or if the child is unstable a further bolus of IV hydrocortisone as outlined in the major surgery guidance is required.

British Society of Paediatric Endocrinology & Diabetes Adrenal Insufficiency Guidance: : (**link**)		
Hydrocortisone dose for minor procedures requiring general anaesthesia		
	Hydrocortisone bolus dose	**Post-operative**
Induction	2mg /kg (max 100mg) * (4mg/kg in neonates)	Oral sick day steroid doses for 24 hours
* It would seem prudent to use the neonatal dosing for infants who are significantly small for gestational age or failing to thrive and as such, whilst not neonates, are a neonatal size		

4.2 Minor procedures NOT requiring general anaesthesia

British Society of Paediatric Endocrinology & Diabetes Adrenal Insufficiency Guidance: : (**link**)	
Hydrocortisone advice for minor procedures NOT requiring general anaesthesia	
Medical procedures (local anaesthetic or sedation)	**Oral hydrocortisone dose**
Minor procedure – local anaesthetic (e.g. skin biopsy) Minor dental procedures e.g. filling, tooth extraction	Give oral sick day steroid dose prior to procedure. Continue for up to 24 hours if in pain or unwell
MRI scans (using sedation) Non-anaesthetic sedation (e.g. chloral hydrate) does not merit use of IV hydrocortisone. Sick day dosing with oral hydrocortisone is sufficient	Give oral sick day steroid dose prior to procedure and continue for the day

Table 5: Checklist for information, Education and Training required prior to initial discharge / at time of diagnosis

Information, Education and Training required prior to initial discharge / at time of diagnosis	
Written information about adrenal insufficiency (e.g.: BSPED website (**link**), ESPE, SPEG)	
Recommend use of BSPED AI card website hyperlink (or equivalent) which covers the information below: • Current steroid treatment plan and doses (and mineralocorticoid if relevant) • Sick day episode oral steroid dose • Emergency intramuscular steroid dose	
Emergency hydrocortisone injection kits (for home, nursery/school and any other regular residence (grandparents, parents / carers not co-habiting)	
Training to administer hydrocortisone injection (in person, virtual, YouTube) https://www.pituitary.org.uk/news/2020/08/hydrocortisone-injection-video (Solu-cortef; hydrocortisone sodium succinate - powder for dilution) https://www.youtube.com/watch?v=R5_BScN6HwE (Glass vial: hydrocortisone sodium phosphate)	
Open access to local paediatric medical ward / paediatric emergency department	
Provide information for appropriate support group if applicable. livingwithCAH.com, addisonsdisease.org.uk, pituitary.org.uk	
Emergency contact numbers for local paediatric team and regional paediatric endocrinology team if applicable.	
Registered with the ambulance service (Red alert category)	
Medical alert added to notes / electronic hospital systems to flag that child has adrenal insufficiency	
Advice to wear a medical alert bracelet / necklace	
Inform GP of diagnosis, glucocorticoid doses (including sick day episodes) and request glucocorticoids put on repeat a prescription	
Care plan for school / nursery	
Ensure clinic appointment in place with medical staff	
Recommended actions for family	
Download MyCortisol app	
Inform nursery / school	
Ensure adequate supplies of hydrocortisone for sick days and travel	
Medical alert bracelets / necklace / mobile phone medical ID	
Contact appropriate patient support group	
Regularly check that hydrocortisone injections are in date	
Subsequent visits (frequency dependent upon patient's needs)	
Review child/young person and family understanding of condition and sick day rules	
Review BSPED AI leaflet and update daily replacement, sick day episode & emergency IM doses based on up to date measurements.	
Ensure appropriate supply of medication/equipment and training up to date	
Ensure alerts remain in place (Ambulance/patient notes/personal alert for e.g. jewellery or phone)	
Check care plans for school / nursery are up to date	
Review how any sick days were managed. Check if emergency hydrocortisone was required	

Supplementary Materials

Supplementary Table 1: Patient Information: Sick days: When to give additional steroids

Patient Information: Sick days: When to give additional steroids British Society of Paediatric Endocrinology & Diabetes Adrenal Insufficiency Guidance: : (**link**)			
Situation	**Change to usual steroid dose**	**Length of change**	**When to get help?**
Minor Illness			
Mild cold / runny nose with no fever. Minor playground bumps and bruises	No change		
Moderate or severe illness			
Fever, flu, infection, childhood illnesses (usually not well not enough to go to school)	Sick day doses required	For as long as the illness lasts	Contact GP or medical team if not improving after 24-48 hours
Vomiting or diarrhoea	Sick day doses required		
	If sick day dose tolerated (kept down for at least 30 minutes with no frequent diarrhoea or vomiting), then continue oral sick day dosing		
	If sick day dose not tolerated, give intramuscular (IM) hydrocortisone injection		Dial 999 and inform them that the patient is having an adrenal crisis
Drowsy and unresponsive	Give IM hydrocortisone injection		
Major trauma or severe shock (e.g. suspected fracture, road traffic accident, head injury with loss of consciousness).	Give IM hydrocortisone injection		
Other (discuss with medical team)			
Routine or travel vaccinations	Consider 1 or 2 doses of sick day steroids.	Continue if unwell	
Long haul flights	Give usual morning dose at 6 to 8 hourly intervals		
Child or centre specific recommendations			
Surgical and dental procedures			
Minor surgery **(e.g. tooth extraction under local anaesthetic)**	Sick day dose prior to procedure. Return to usual dose immediately afterwards.	Continue sick day doses for up to 24 hours if in pain or unwell	Inform medical staff including dentist and anaesthetist that you/your child have adrenal insufficiency and takes steroids
Major surgery **(e.g. operation requiring general anaesthetic)**	Sick day oral steroids on day of procedure even when fasting. Intravenous (IV) hydrocortisone will be given a little before putting your child to sleep and during surgery, and after surgery if needed	As per local policy or contact treatment centre for advice	

Supplementary Material 2: Pre-calculated oral hydrocortisone sick day episode doses

A total daily hydrocortisone dose of around 30/mg/m^2/day given as four evenly spaced doses is recommended for illness. A guide to the doses is provided below; however the actual dose may vary depending on the strength and preparation of the available hydrocortisone medication.

A pragmatic approach for convenience may be to divide the total daily sick day steroid dose according to the strength of the immediate release hydrocortisone preparation prescribed (for example if the child or young person uses hydrocortisone 10mg tablets and the sick day dose is 12.5mg - four times a day, then it may be more practical to give 20mg in the morning or onset of illness followed by 10mg for the other three doses).

Weight (kg)	BNFc surface area	Total daily sick day steroid dose (mg) (30/m^2/day)	**Sick day hydrocortisone: Dose**	**Frequency**
1	0.1	3	**0.8**	4 x a day
2	0.16	5	**1.2**	4 x a day
3	0.21	6	**1.5**	4 x a day
4	0.26	8	**2**	4 x a day
5	0.3	9	**2.5**	4 x a day
6	0.34	10	**2.5**	4 x a day
7	0.38	11	**3**	4 x a day
8	0.42	13	**3**	4 x a day
9	0.46	14	**3.5**	4 x a day
10	0.49	15	**4**	4 x a day
15	0.65	20	**5**	4 x a day
20	0.79	24	**6**	4 x a day
25	0.92	28	**7.5**	4 x a day
30	1.1	33	**7.5**	4 x a day
35	1.2	36	**10**	4 x a day
40	1.3	39	**10**	4 x a day
45	1.4	42	**10**	4 x a day
50	1.5	45	**10**	4 x a day
55	1.6	48	**12.5**	4 x a day
60	1.7	51	**12.5**	4 x a day
65	1.8	54	**12.5**	4 x a day
70	1.9	57	**15**	4 x a day
75	1.9	57	**15**	4 x a day
80	2.1	63	**15**	4 x a day
90	2.2	66	**15**	4 x a day

Supplementary material 3: Management of fluid and electrolyte abnormalities in primary and secondary AI

	Primary adrenal insufficiency (elevated ACTH levels)	**Secondary adrenal insufficiency** (suppressed ACTH)
Glucocorticoid treatment	Usually Hydrocortisone	Usually Hydrocortisone (or Prednisolone)
Mineralocorticoid treatment	Fludrocortisone	Not required
	Acute illness (primary AI)	**Acute illness (secondary AI)**
Possible abnormality of sodium and potassium	May have hyponatraemia and hyperkalaemia. Dehydration is due to mineralocorticoid deficiency causing salt and water loss.	ACTH and hence cortisol deficiency is associated with an inability to excrete a water load. Hyponatraemia, if present may be due to excess water. Potassium is usually normal. Thus patients may not be significantly fluid deplete.
Other possible electrolyte abnormalities	Hypoglycaemia Hypercalcaemia Metabolic acidosis	Hypoglycaemia
Treatment	Correct hypoglycaemia Glucocorticoids in stress doses have some mineralocorticoid action. Sick day oral hydrocortisone or intravenous hydrocortisone along with IV 0.9% NaCl will usually result in resolution of biochemical abnormality. In some cases, specific treatment for hyperkalaemia is required (see below)	Correct hypoglycaemia The volume and type of IV fluid may need to be adapted to the individual circumstance. This may include checking that adequate glucocorticoids have been provided For further details see below

Features warranting slow or particularly careful rehydration in hyponatraemia

Rapid correction of acute and chronic hyponatraemia can be associated with a significant risk of cerebral oedema and / or osmotic demyelination syndrome. There is a substantial risk of seizures with plasma Na <110 mmol/l and an elevated risk of the osmotic demyelination syndrome if plasma Na concentration <105 mmol/l.

A careful approach to rehydration is therefore needed in children with:

a) Severe hyponatraemia; plasma sodium < 120 mmol/l.
b) Reduced consciousness, seizures or other signs compatible with cerebral oedema.
c) Diabetes insipidus
d) When duration of illness or being unwell is more than one day

Key considerations in severe hyponatraemia

a) Avoid increasing plasma Na concentration by >10 mmol/l/day (~0.5 mmol/l/hr) in these circumstances. Normal (0.9%) saline with stress doses of glucocorticoid can increase sodium concentrations more rapidly than this. Therefore, the IV fluid may need to be changed to one containing less sodium.
b) A slow, measured, increase in serum sodium can be achieved by linking sodium input (fluid) to output (urine). (i.e. giving a little more sodium than that present in the urine.)
c) In patients in adrenal crisis careful monitoring of electrolytes is required. This is particularly important when hydrocortisone treatment is started because in addition to its' mineralocorticoid action, hydrocortisone will also switch off ADH secretion leading to a diuresis and potentially a rapid rise in plasma sodium concentration.
d) 1 ml /kg of 3% saline will increase the plasma Na concentration by about 1 mmol/l. This can be considered especially in the context of abnormal neurology or on-going severe symptomatic hyponatraemia. This bolus may need to be repeated. Close supervision and regular clinical assessment and monitoring of electrolytes is required.
e) Consider admission to PHDU/PICU
f) The rate of correction of hyponatraemia may be dependent on the underlying aetiology. The sodium should not rise >10mmol/l in 24 hours.

g)	**Hyperkalaemia treatment**
	a) Rehydration with sodium chloride and the administration of hydrocortisone are key measures that will reduce potassium in the context of AC b) If plasma potassium is > 7.0 nmol/L or there are ECG changes – IV 10% calcium gluconate: 0.5 ml/kg (0.11 mmol/kg) slow IV administration over 10 minutes with ECG monitoring to stabilise myocardium. Maximum single dose 4.5 mmol (20 ml) c) Nebulised salbutamol is a quick and readily available treatment that drives potassium into cells – 0 - 5 years: 2.5 mg; ≥5 years: 5 mg (three doses back-to-back). d) If persistent hyperkalaemia - Insulin and Dextrose – short-acting insulin (Actrapid or Novorapid): 0.1 units/kg in 5 to 10 ml/kg of 10% dextrose IV over 30 minutes e) If significant metabolic acidosis, consider sodium bicarbonate 1 mmol/kg IV over 30 minutes f) Consider cation exchange resins – calcium or sodium polystyrene sulfonate (resonium) – 125 to 250 mg/kg QDS orally or PR in neonates. g) Consider admission to PHDU/PICU. Potassium levels must be checked within 15 minutes post treatment and 1-2 hours after treatment.

Supplementary material 4: Reference table for comparison of hydrocortisone bolus doses based on weight and surface area for neonates, children and teenagers

Hydrocortisone doses do not alter after the young person reaches a weight of 50kg
The doses in the dark grey shaded boxes are not applicable and are only shown for reference

Comparison of hydrocortisone bolus doses based on weight and surface area

Neonates 4mg/kg initial bolus followed by 2mg/kg QDS. Children 2mg/kg initial bolus followed by 1mg/kg QDS *

					Dose/day			Dose/day			Dose/day
Age	**Weight (kg)**	**BNFc SA**	**1mg/kg**	**dose/m^2**	**24 hrs/m^2**	**2mg/kg**	**dose/m^2**	**24hrs/m^2**	**4mg/day**	**dose/m^2**	**24hrs/m2**
prem	1	0.1	1	10	40	2	20	80	4	40	160
prem	2	0.16	2	13	50	4	25	100	8	50	200
neonate	3	0.21	3	14	57	6	29	114	12	57	229
neonate	4	0.26	4	15	62	8	31	123	16	62	246
Infant	5	0.3	5	17	67	10	33	133	20	67	267
infant	6	0.34	6	18	71	12	35	141	24	71	282
Infant	7	0.38	7	18	74	14	37	147	28	74	295
infant	8	0.42	8	19	76	16	38	152	32	76	305
Infant	9	0.46	9	20	78	18	39	157	36	78	313
infant	10	0.49	10	20	82	20	41	163	40	82	327
child	15	0.65	15	23	92	30	46	185	60	92	369
child	20	0.79	20	25	101	40	51	203	80	101	405
child	25	0.92	25	27	109	50	54	217	100	109	435
child	30	1.1	30	27	109	60	55	218	120	109	436
teen	40	1.3	40	31	123	80	62	246	160	123	492
teen	50	1.5	50	33	133	100	67	267	200	133	533
teen	60	1.7	50	29	118	100	59	235	240	141	565
adult	70	1.9	50	26	105	100	53	211	280	147	589
adult	90	2.2	50	23	91	100	45	182	360	164	655

***** It would seem prudent to use the neonatal dosing for infants who are significantly small for gestational age or failing to thrive and as such, whilst not neonates, are a neonatal size

Surface area based schedules often utilise 50 - 100mg/m^2 divided into 4 doses.

Neonates: induction dose of 4mg/kg followed by 2mg/kg every 6 hours
Neonates: 2mg/kg every 6 hours provides a 24 hour dose of 80 to 123mg/m^2/day

At some weight bands the dose may be more generous. This is based on the presumption that there is on-going hydrocortisone treatment every 6 hours. In reality there is likely to be on-going review and modification

Worked examples
3kg term infant: 4mg/kg/bolus, followed by 2mg/kg every 6 hours (based on surface area they get 57, 29, 29, 29 = 144mg/m^2/day)

6kg infant (2 months old): 2mg/kg, followed by 1mg/kg every 6 hours (base on surface area they get 35, 18. 18. 18 = 89mg/m^2/day) - with a caveat that they can have 2mg/kg if unstable or at 4 hourly

Supplementary material 5: Clinic review checklist

Example checklist					
Name: **DOB / identifier:** **Cause of Adrenal Insufficiency:**					
	Y / N / n/a	**Comments**	**Parent/ Guardian signature**	**Health professional signature**	**Follow Up**
Patient/Parent information leaflet provided					
Discussion re: Sick day episode management					
Adrenal insufficiency information for school given to family					
BSPED Sick day steroid management card provided					
IM hydrocortisone kit provided / advised GP					
IM Hydrocortisone teaching					
Ambulance alert added					
Hospital alert added to patient notes					

References

Ali SR, Bryce J, Haghpanahan H, Lewsey JD, Tan LE, Atapattu N, Birkebaek NH, Blankenstein O, Neumann U, Balsamo A, Ortolano R, Bonfig W, Claahsen-van der Grinten HL, Cools M, Costa EC, Darendeliler F, Poyrazoglu S, Elsedfy H, Finken MJJ, Fluck CE, Gevers E, Korbonits M, Guaragna-Filho G, Guran T, Guven A, Hannema SE, Higham C, Hughes IA, Tadokoro-Cuccaro R, Thankamony A, Iotova V, Krone NP, Krone R, Lichiardopol C, Luczay A, Mendonca BB, Bachega TASS, Miranda MC, Milenkovic T, Mohnike K, Nordenstrom A, Einaudi S, van der Kamp H, Vieites A, de Vries L, Ross RJM, Ahmed SF. Real-World Estimates of Adrenal Insufficiency-Related Adverse Events in Children With Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2021 Jan 1;106(1):e192-e203. doi: 10.1210/clinem/dgaa694. PMID: 32995889; PMCID: PMC7990061.

Ali SR, Bryce J, Krone NP, Claahsen van der Grinten HL, Ahmed SF. Management Of Acute Adrenal Insufficiency Related Adverse Events In Children With Congenital Adrenal Hyperplasia - Results Of An International Survey Of Specialist Centres. Horm Res Paediatr. 2022 May 13. doi: 10.1159/000525075. Epub ahead of print. PMID: 35569445.

Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015 Mar;172(3):R115-24. doi: 10.1530/EJE-14-0824. Epub 2014 Oct 6. PMID: 25288693.

BSPED Paediatric Steroid Treatment Card
https://www.bsped.org.uk/media/ewaphps5/bsped-adrenal-insufficiency-card.pdf

BNFc: https://bnfc.nice.org.uk/drugs/hydrocortisone/

Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, Arlt W, Auchus RJ, Falhammar H, Flück CE, Guasti L, Huebner A, Kortmann BBM, Krone N, Merke DP, Miller WL, Nordenström A, Reisch N, Sandberg DE, Stikkelbroeck NMML, Touraine P, Utari A, Wudy SA, White PC. Congenital Adrenal Hyperplasia-Current Insights in Pathophysiology, Diagnostics, and Management. Endocr Rev. 2022 Jan 12;43(1):91-159. doi: 10.1210/endrev/bnab016. PMID: 33961029; PMCID: PMC8755999.

Goldbloom EB, Mokashi A, Cummings EA, Abish S, Benseler SM, Huynh HQ, Watson W, Ahmet A. Symptomatic adrenal suppression among children in Canada. Arch Dis Child. 2017 Apr;102(4):338-339. doi: 10.1136/archdischild-2016-311223. Epub 2016 Nov 9. PMID: 28320817.

Hindmarsh PC, Charmandari E. Variation in absorption and half-life of hydrocortisone influence plasma cortisol concentrations. Clin Endocrinol (Oxf). 2015 Apr;82(4):557-61. doi: 10.1111/cen.12653. Epub 2014 Dec 19. PMID: 25369980.

National child measurement programme 2020/21
https://digital.nhs.uk/data-and-information/publications/statistical/national-child-measurement-programme/2020-21-school-year

National Reporting and Learning System (NRLS)
https://www.england.nhs.uk/patient-safety/monthly-data-patient-safety-incident-reports/

National Institute of Clinical Excellence (NICE)
https://www.nice.org.uk/guidance/ng80/evidence/chronic-asthma-management-pdf-7079863934

Neonatal and Paediatric Pharmacy Group (NPPG)

http://nppg.org.uk/wp-content/uploads/2021/12/Position-Statement-Steroid-Cards-V1.pdf

NHS England Safety Alert: 13/8/2020: Reference no: NatPSA/2020/005/NHSPS https://www.england.nhs.uk/wp-content/uploads/2020/08/NPSA-Emergency-Steroid-Card-FINAL-2.3.pdf

Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. Cochrane Database Syst Rev. 2020 Mar 19;3(3):CD012517. doi: 10.1002/14651858.CD012517.pub2. PMID: 32190901; PMCID: PMC7081382.

Nowotny H, Ahmed SF, Bensing S, Beun JG, Brösamle M, Chifu I, Claahsen van der Grinten H, Clemente M, Falhammar H, Hahner S, Husebye E, Kristensen J, Loli P, Lajic S, Reisch N; Endo ERN (MTG1). Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis. Endocrine. 2021 Mar;71(3):586-594. doi: 10.1007/s12020-021-02649-6. Epub 2021 Mar 4. PMID: 33661460; PMCID: PMC7929907.

Odenwald B, Nennstiel-Ratzel U, Dörr HG, Schmidt H, Wildner M, Bonfig W. Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life. Eur J Endocrinol. 2016 Feb;174(2):177-86. doi: 10.1530/EJE-15-0775. Epub 2015 Nov 12. PMID: 26563979.

Peters CJ, Hill N, Dattani MT, Charmandari E, Matthews DR, Hindmarsh PC. Deconvolution analysis of 24-h serum cortisol profiles informs the amount and distribution of hydrocortisone replacement therapy. Clin Endocrinol (Oxf). 2013 Mar;78(3):347-51. doi: 10.1111/j.1365-2265.2012.04502.x. PMID: 22803584.

Prete A, Taylor AE, Bancos I, Smith DJ, Foster MA, Kohler S, Fazal-Sanderson V, Komninos J, O'Neil DM, Vassiliadi DA, Mowatt CJ, Mihai R, Fallowfield JL, Annane D, Lord JM, Keevil BG, Wass JAH, Karavitaki N, Arlt W. Prevention of Adrenal Crisis: Cortisol Responses to Major Stress Compared to Stress Dose Hydrocortisone Delivery. J Clin Endocrinol Metab. 2020 Jul 1;105(7):2262–74. doi: 10.1210/clinem/dgaa133. PMID: 32170323; PMCID: PMC7241266.

Rezai M, Fullwood C, Hird B, Chawla M, Tetlow L, Banerjee I, Patel L. Cortisol Levels During Acute Illnesses in Children and Adolescents: A Systematic Review. JAMA Netw Open. 2022 Jun 1;5(6):e2217812. doi: 10.1001/jamanetworkopen.2022.17812. PMID: 35731516; PMCID: PMC9218852.

Rubens M, Kanaris C. Fifteen-minute consultation: Emergency management of children presenting with hyperkalaemia. Arch Dis Child Educ Pract Ed. 2021 Aug 3:edpract-2021-322080. doi: 10.1136/archdischild-2021-322080. Epub ahead of print. PMID: 34344762.

Rushworth RL, Torpy DJ, Stratakis CA, Falhammar H. Adrenal Crises in Children: Perspectives and Research Directions. Horm Res Paediatr. 2018;89(5):341-351. doi: 10.1159/000481660. Epub 2018 Jun 6. PMID: 29874655.

Rushworth RL, Torpy DJ, Falhammar H. Adrenal Crisis. N Engl J Med. 2019 Aug 29;381(9):852-861. doi: 10.1056/NEJMra1807486. PMID: 31461595.

SIGN https://www.sign.ac.uk/media/1773/sign158-updated.pdf

Shulman DI, Palmert MR, Kemp SF; Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics. 2007 Feb;119(2):e484-94. doi: 10.1542/peds.2006-1612. Epub 2007 Jan 22. PMID: 17242136.

Simpson H, Tomlinson J, Wass J, Dean J, Arlt W. Guidance for the prevention and emergency management of adult patients with adrenal insufficiency. Clin Med (Lond). 2020 Jul;20(4):371-378. doi: 10.7861/clinmed.2019-0324. PMID: 32675141; PMCID: PMC7385786.

Swerdlow AJ, Higgins CD, Brook CG, Dunger DB, Hindmarsh PC, Price DA, Savage MO. Mortality in patients with congenital adrenal hyperplasia: a cohort study. J Pediatr. 1998 Oct;133(4):516-20. doi: 10.1016/s0022-3476(98)70060-5. PMID: 9787690.

Woodcock T, Barker P, Daniel S, Fletcher S, Wass JAH, Tomlinson JW, Misra U, Dattani M, Arlt W, Vercueil A. 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. Anaesthesia. 2020 May;75(5):654-663. doi: 10.1111/anae.14963. Epub 2020 Feb 3. Erratum in: Anaesthesia. 2020 Sep;75(9):1252. PMID: 32017012.

Worth C, Vyas A, Banerjee I, Lin W, Jones J, Stokes H, Komlosy N, Ball S, Clayton P. Acute Illness and Death in Children With Adrenal Insufficiency. Front Endocrinol (Lausanne). 2021 Oct 13;12:757566. doi: 10.3389/fendo.2021.757566. PMID: 34721304; PMCID: PMC8548653.