REVIEW

DOI: 10.4274/jcrpe.galenos.2024.2024-6-12-S

J Clin Res Pediatr Endocrinol 2025;17(Suppl 1):80-92

Treatment and Prevention of Adrenal Crisis and Family Education

Emine Çamtosun[1], Özlem Sangün[2]

[1]İnönü University Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Turkey
[2]Başkent University Faculty of Medicine, Department of Pediatric Endocrinology, Adana, Turkey

Abstract

Adrenal crisis is a life threatening complication of adrenal insufficiency (AI). Its treatment is urgent and parenteral hydrocortisone (HC) should be given at 10-15 times physiological doses in this situation. If HC is not available, alternatively prednisolone or methyl prednisolone may be used. In cases where peripheral venous access cannot be achieved quickly, intramuscular (IM) administration should be performed without delay. Fluid deficit, hypoglycemia, hyponatremia and hyperkalemia should be evaluated and corrected. Stressful conditions, such as physical stress, accidents, injuries, surgical interventions and anesthesia increase the need for cortisol and may lead the development of adrenal crisis. In order to prevent adrenal crisis, glucocorticoid dose should be increased according to the magnitude and severity of the stress situation as described in this review. Patients' and/or their families' education may improve the management of AI and reduce the frequency of adrenal crisis and/or mortality. They should be trained about conditions leading to adrenal crisis, how to increase the glucocorticoid dose in stress situations, recognizing signs of adrenal crisis and using IM HC if it is needed. All patients should be encouraged to carry a card/information sheet/medical alert bracelet or necklace indicating the diagnosis of AI and need for HC administration. It is useful for patients and parents to have an emergency glucocorticoid injection kit and to receive self-injection training.

Keywords: Adrenal crisis, treatment, prevention, stress, family education

Introduction

Adrenal crisis is the most frightening complication of adrenal insufficiency (AI). The annual incidence has been reported as 4.4-17/100 patient years, and 1/200 cases of adrenal crisis result in death every year (1). Acute adrenal crisis usually occurs when a child with undiagnosed chronic AI is exposed to additional stress. Various infections, especially respiratory infections in early childhood and gastrointestinal infections in older ages, play an accelerating role in the emergence of adrenal crisis (2,3). Furthermore, any condition that increases the need for cortisol, like physical stress, accidents, injuries, surgical interventions and anesthesia may lead the development of adrenal crisis (4).

There is no agreement upon the definition of adrenal crisis. It is considered to be acute clinical deterioration of a patient with AI (5). A definition of adrenal crisis in adults has been reported as the presence of at least two of the following symptoms or findings: hypotension, nausea/vomiting, severe weakness, hyponatremia, hypoglycaemia and hyperkalemia, as well as deterioration in general health and well-being. Adrenal crisis may be the first clinical presentation of undiagnosed AI. Signs and symptoms of AI and adrenal crisis are summarized in Table 1.

In individuals without AI, glucocorticoid release is increased in situations that stress the body (anesthesia, surgery, major trauma, febrile infections, sepsis, and so on) (3,6,7,8,9,10,11). Since endogenous glucocorticoid release cannot increase during stressful situations in individuals

Cite this article as: Çamtosun E, Sangün Ö. Treatment and prevention of adrenal crisis and family education. J Clin Res Pediatr Endocrinol. 2025;17(Suppl 1):80-92

Address for Correspondence: Emine Çamtosun Assoc. Prof. MD, İnönü University Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Turkey
E-mail: epurcuklu@gmail.com **ORCID:** orcid.org/0000-0002-8144-4409

Conflict of interest: None declared
Received: 14.06.2024
Accepted: 31.10.2024
Epub: 23.12.2024
Publication date: 10.01.2025

with AI, the glucocorticoid dose should be increased to the stress dose to prevent the onset of AI symptoms and adrenal crisis (3,12,13). Two case reports published in 1952 and 1953 reported that a patient on chronic steroid treatment died of cardiovascular collapse related to secondary AI after surgery, which was considered to be the first evidence of this (14). There are no randomised controlled trials investigating the dose of glucocorticoids that should be given in stressful situations that increase cortisol requirements in children with AI. As it is thought that unnecessarily high doses of glucocorticoids may cause side effects, such as hyperglycaemia, impaired wound healing, increased risk of infection, gastrointestinal ulcers, osteopenia, growth suppression and adipogenesis, it is important to determine the actual dose required in stressful situations (15,16). However, it is suggested that preventing the negative effects associated with insufficient steroid use is more important than the problems that may arise from short-term high dose steroid use (3).

The most important way to protect patients from life-threatening adrenal crisis is to ensure patient awareness through appropriate education (2,17). Education of children with AI and/or their families about the diagnosis and treatment, stressful situations, and how to increase the dose of steroids in stressful situations, may improve management of the disease and reduce the frequency of adrenal crisis. Training them to recognize symptoms of adrenal crisis and using intramuscular (IM) hydrocortisone (HC) if it is needed may reduce morbidity and mortality. It is important to repeat training periodically. When the patients with known AI are evaluated 6 months after a three-hour training session, it was found that they gave significantly more accurate answers to scenarios in which a possible adrenal crisis could develop (18). It is appropriate for patients/caregivers to have a written document or identification material (card, medical alert bracelet etc.) to be shown to the first consulted healthcare professional regarding what can be done in emergency situations.

Since AI and its complications are rare life-threatening conditions, it is important to ensure standardised approaches by physicians in its management. This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for "Treatment and Prevention of Adrenal Crisis and Family Education" in children and adolescents with AI. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

Treatment of Adrenal Crisis

Adrenal crisis may be the first sign of AI. Symptoms such as fatigue, weakness, tachycardia, hypotension, nausea, vomiting, abdominal pain and seizures generally respond very quickly to parenteral HC administration. If it is not recognized and treated quickly, coma and death may occur (19). For these reasons, adrenal crisis treatment should never be delayed for reasons such as waiting for test results. However, it is extremely important to take a blood sample for diagnostic tests, especially basal serum cortisol and ACTH levels, before treatment (3). Achieving clinical improvement after HC administration is considered as an essential diagnostic criterion (20).

Since adrenal crisis is a life-threatening situation, treatment should not be delayed (3,21). An example for algorithm of AI treatment for emergency department can be seen in Figure 1. Although the intravenous (IV) route is preferred in hospital conditions, IM administration is also effective in cases where vascular access cannot be established (4).

Table 1. Clinical findings of adrenal insufficiency and adrenal crisis* (3)

	Symptom	Finding	Laboratory
Adrenal insufficiency	Weakness	Hyperpigmentation (PAI only)	Hyponatremia
	Weight loss	Growth failure	Hyperkalemia
	Postural dizziness	Low blood pressure	Hypoglycemia
	Anorexia, abdominal discomfort		Occasionally hypercalcemia
Adrenal crisis	Severe weakness, syncope	Hypotension	Hyponatremia
	Abdominal pain, nausea, vomiting, sometimes back pain	Abdominal sensitivity, defence	Hyperkalemia
	Confusion	Confusion, delirium	Hypoglycemia
			Rare hypercalcemia

*Since many symptoms are non-specific and have been present for a long time, there are often delays in diagnosis. Hyponatremia and hyperkalemia often mediate the diagnosis. Hyperpigmentation is a specific finding but varies among individuals and requires comparison with the individual's past pigmentation status. Adrenal crisis requires emergency treatment. Preventing adrenal crisis is an important part of patient management. Findings of autoimmune diseases that may accompany adrenal insufficiency, neurological findings in patients with adrenoleukodystrophy, and findings of diseases that cause adrenal infiltration may also be observed.
PAI: primary adrenal insufficiency

Regardless of the route of administration, HC absorption occurs at similar levels (22).

It is known that the level of endogenous cortisol increase in acute stress situations, such as critical illness, anesthesia, and surgery, varies greatly from patient to patient (8,9,23). It is thought that increased glucocorticoid secretion during critical illnesses is necessary for the proper functioning of defense mechanisms (such as cytokine release) as well as to prevent the negative physiological changes that may occur due to excessive stress response (24). There are no randomized clinical studies examining the glucocorticoid doses that should be used in cases where cortisol requirement increases. However, it is thought that this need is directly proportional to the duration and severity of the stressful situation. Traditionally, it is estimated that adults will release 75-100 mg/day of cortisol in major surgery and 50 mg/day in minor surgery. It has been observed that cortisol release rarely exceeds 200 mg per day after some procedures (11). The purpose of using these high doses is not only to mimic the cortisol response in normal individuals, but also to meet unexpected needs that may arise as a result of complications. There is no direct evidence to suggest that these doses are harmful or that lower doses are safe. It is known that approximately 50 mg of HC is equivalent to 100 mcg fludrocortisone (25). Since sufficient mineralocorticoid effect is achieved when approximately 50 mg/day HC is used, additional mineralocorticoid use is not recommended at these doses (3,23). If a cause, such as infection, that triggers adrenal crisis is present, that should be treated separately (26).

Glucocorticoids are secreted into the systemic circulation in a pulsatile and circadian manner. Cortisol release rate has not been found to be related to gender or pubertal status in children (27). A person with normal adrenal function secretes cortisol approximately 5-10 mg/m^2/day (28). Under conditions of stress, cortisol release rate can increase up to 10-15 times. Insufficient use of glucocorticoids during adrenal crisis are potentially dangerous. However, there are no systematic dose-response studies done on this subject, and the recommended glucocorticoid doses in treatment are largely empirical.

In the treatment of adrenal crisis, a continuous infusion of HC 2 mg/kg/day can be performed after administration of HC IV bolus 4 mg/kg, until stabilization is achieved.

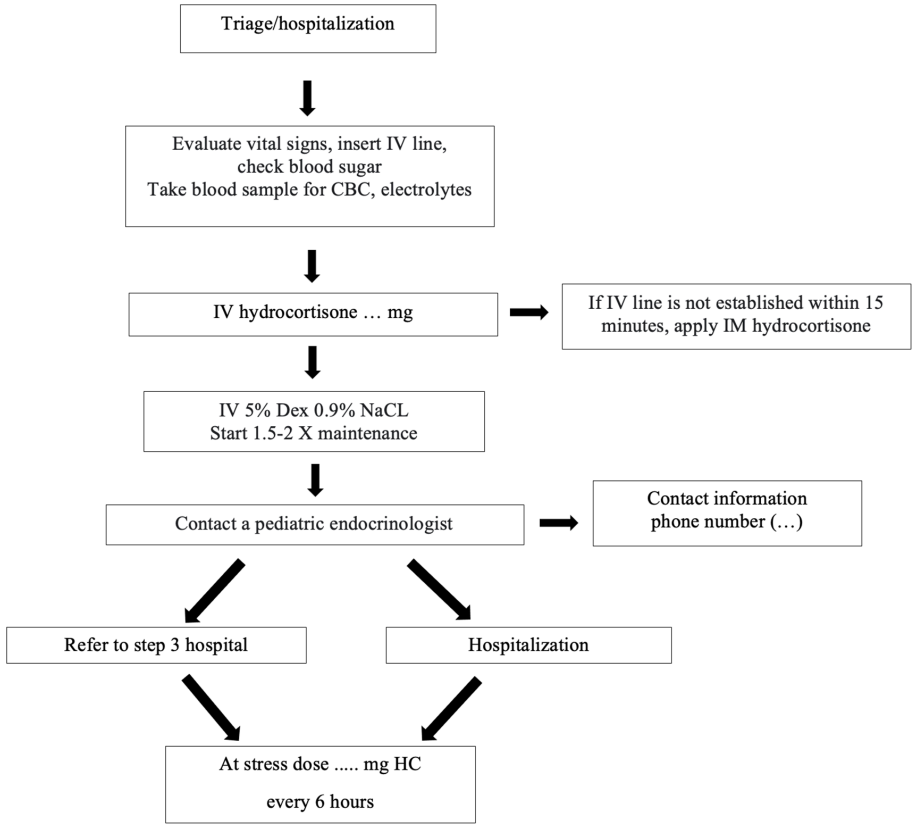

Figure 1. Algorithm sample of adrenal insufficiency treatment for emergency department (4)

HC: hydrocortisone, IV: intravenous, IM: intramuscular, SC: subcutaneous, CBC: complete blood count

Alternatively, the same dose can be divided and IV/IM bolus can be applied at 4-6 hour intervals. Initial administration of 50-100 mg/m^2 HC bolus followed by 50-75-100 mg/m^2/day continuous infusion or at 6-hour intervals has also been suggested (21). When the bolus dose is adjusted according to age and body surface practically, the dosing regimens are: children under two years of age/weighing < 15 kg, between 2-6 years of age/weighing 15-25 kg and over six years of age/weighing more than 25 kg, doses are 25, 50 and 100 mg HC, respectively (21). In cases where peripheral venous access cannot be achieved quickly, IM administration should be performed without delay.

It is recommended to avoid synthetic, long-acting steroids, such as dexamethasone in childhood (3,20). HC and prednisolone are active glucocorticoids. Cortisone acetate and prednisone are activated by hepatic 11 beta hydroxy steroid dehydrogenase. The use of inactive precursor glucocorticoids may show greater pharmacokinetic changes due to individual differences. However, this issue has not been studied systematically (3).

If HC is not available, prednisolone can be used as an alternative. Dexamethasone should not be used, except as a last resort, as it has a high growth suppressant effect but a very low mineralocorticoid effect (3). Prednisolone has four times the glucocorticoid activity of HC, and methylprednisolone has five times the glucocorticoid activity. Therefore, if prednisolone is to be used, the dose should be calculated as 1/4, and if methylprednisolone is to be used, the dose should be 1/5 of the HC dose (20,21). Although the use of steroids other than HC is not recommended, in cases where there is no other option, calculation of the equivalent doses of the other steroids is needed (29).

Dehydration, hypoperfusion and hypotension may occur in glucocorticoid and mineralocorticoid deficiency. If there is hypotension, 0.9% saline bolus can be given at a dose of 20 mL/kg; in case of shock, this dose can be increased up to 60 mL/kg in one hour (3,4,30,31).

The amount of IV fluid to be given during adrenal crisis treatment is calculated as maintenance + deficit and can be adjusted as 150-180 mL/kg/day in newborns and 2.5-3 liters/m^2/day in older children, depending on the age and needs of the patient (20,21). For this purpose, 5% Dextrose 0.9% NaCl (or 5% Dextrose 0.45% NaCl) is often the appropriate treatment option (3,21). Deficit treatment replaces the fluid lost by the patient according to the degree of dehydration. In order to calculate the deficit fluid, the patient's weight and degree of dehydration must be known (32). Assessment of clinical dehydration can sometimes be misleading, and patients need to be closely monitored and fluid needs should be re-evaluated during treatment. The patient's fluid and electrolyte therapy should be rearranged according to clinical and biochemical monitoring (such as blood pressure, heart rate, urine output, state of consciousness, glucose level) (33).

Glucocorticoids play an important role in maintaining blood glucose balance. Hypoglycemia, a symptom of acute AI, is more common in children than adults. Blood glucose should be monitored hourly (21). In case of hypoglycemia, IV bolus 10% Dextrose given at a dose of 2-10 mL/kg should be continued with a fluid containing 5% or 10% Dextrose to maintain normoglycemia, depending on the patient's blood glucose level. If it is needed, 25% Dextrose (0.5-1 g/kg, maximum 25 g at a time, at a rate of 2-3 mL/hour) can be given using a central vein (3,4,21,30,31).

Sodium and potassium levels should be monitored carefully (21). Hyponatremia is the most consistent biochemical finding seen in acute AI (34). Sodium is the dominant cation of extracellular fluid and is very important for maintaining intravascular volume as it is the determinant of osmolality. Hyponatremia in AI occurs due to renal losses as a result of glucocorticoid and mineralocorticoid deficiency (32). To correct hyponatremia, 10-15 mEq/kg/day NaCl can be given in rehydration fluids containing Dextrose, but the rate of increase in plasma sodium level should not exceed 0.5-1 mEq/hour (10-12 mEq/24 hours or 18 mEq/48 hours). It should be taken into account that sodium levels may rise rapidly when HC is applied. In cases of severe findings, such as seizures, IV hypertonic saline (3% NaCl) is recommended to increase serum sodium and protect against brain edema. Each 1 mL/kg of 3% NaCl increases serum sodium by approximately 1 mEq/L. Clinical improvement is often observed in a child with active symptoms after receiving 4-6 mL/kg of 3% NaCl. Problems such as central pontine myelinosis, which may occur with rapid correction of hyponatremia, are observed during the treatment of chronic hyponatremia rather than acute hyponatremia (3,32).

If patients have severe, symptomatic or persistent hyperkalemia despite HC and rehydration fluid, potassium-lowering agents can be used (35). Clinical symptoms often occur when the potassium level exceeds 7 mmol/L. The most important finding of hyperkalemia is related to the cardiac conduction disorders. When potassium levels are above 6-6.5 mEq/L, an electrocardiogram (ECG) should be taken to evaluate the urgency of the situation. ECG changes begin with a sharpening of the T waves. As potassium levels increase, the P-R interval becomes longer, the P wave

J Clin Res Pediatr Endocrinol
2025;17(Suppl 1):80-92

becomes flatter and the QRS complex expands. Patients might experience palpitations, atrioventricular block, ventricular fibrillation or asystole. Paresthesia, weakness and tingling may be observed in some patients. Cardiac toxicity caused by hyperkalemia increases when accompanied by hyponatremia and metabolic acidosis. Drugs used in the treatment of hyperkalemia are summarized in Table 2 (36,37).

After correction of hypovolemia, hypoglycemia, electrolyte irregularities and clinical improvement, with parenteral treatments, oral HC treatment (30-50 mg/m^2/day) can be started (21). At least three times the usual HC dose should be given on the first day, then gradually reduced over a few days and switched to the normal dose (20). In this case, fludrocortisone (0.05-0.1 mg/day) can be added if necessary. Using dexamethasone alone in glucocorticoid replacement therapy may lead to adrenal crisis because it has no mineralocorticoid effect.

Good practice points:

1. Adrenal crisis treatment is urgent and should never be delayed for reasons such as waiting for test results. However, it is very useful to take a blood sample for diagnostic tests before treatment (1⊕⊕⊕O).

2. In the initial treatment of adrenal crisis, HC bolus 2-4 mg/kg (50-100 mg/m^2) should be started IV. The use of mineralocorticoids is not necessary in a patient receiving a stress dose of HC exceeding 40 mg (1⊕⊕⊕O).

3. If HC is not available, alternatively prednisolone or methylprednisolone may be used. The use of dexamethasone is not recommended (1⊕⊕⊕O).

4. In adrenal crisis, the presence of fluid deficit, hypoglycemia, hyponatremia and hyperkalemia should be evaluated and corrected with appropriate treatment (parenteral fluid support aimed at correcting hypoglycemia, hyponatremia and hyperkalemia) (1⊕⊕⊕O).

Management of Stressful Situations in Patients with Adrenal Insufficiency

Exercise

Exercise is defined as any activity involving the generation of force by activated muscle(s) that results in an alteration of the homeostatic state. In dynamic exercise, the muscle may perform shortening or be overcome by external resistance and perform lengthening. When muscle force results in no movement, the contraction is termed static or isometric. Most activities combine varying amounts of both isometric and dynamic exercise (38). A way to understand and measure the intensity of physical activity is by understanding intensity and how physical activity affects heart rate and breathing. The talk test is a simple way to measure relative intensity. If you can talk and sing during activity you are doing light intensity activity (LIA). Daily activities such as sleeping, watching television, writing, desk work, typing or walking slower than three miles per hour are LIAs. In general, if you're doing moderate-intensity activity (MIA), you can talk but not sing during the activity. Walking briskly (three miles per hour or faster, but not race-walking), water aerobics, bicycling slower than 10 miles per hour on primarily flat or level terrain without hills), tennis (doubles), ballroom dancing, general gardening are examples of MIAs. If you're doing vigorous-intensity activity, you will not be able to say more than a few words without pausing for a breath. For example: race walking, jogging, or running, swimming laps, tennis (singles), aerobic dancing, bicycling 10 miles per hour or faster that may include hills, skipping rope, heavy gardening (continuous digging or hoeing), and hiking uphill or with a heavy backpack (39).

Studies about the need for additional steroids during exercise in children with PAI are lacking. In patients with PAI, the use of an extra dose of HC before short-term intense exercise has not been shown to be superior to placebo in terms of exercise performance and blood glucose levels (40,41). Therefore, the use of extra doses of steroids for short-term exercise is not recommended. There are few published studies on the need for stress dosing in the case of intense, prolonged physical activity (running a marathon, cycling race, ski race, etc.). One study showed healthy athletes exhibited cortisol elevations similar to major surgery after running a marathon (42). Another study reported that healthy athletes participating in ultra marathons were more prone to decreased adrenal responsiveness, and in severe cases, AI (43). In a case report, a 50-year-old male endurance athlete with known PAI reported severe fatigue, nausea, and malaise after competing in prior marathons and intensive endurance exercise. After supplementing with 3-fold daily glucocorticoids and mineralocorticoids before competition, he experienced decreased symptoms and improved performance (44). To better care for these patients, further studies should be conducted to provide safe and effective glucocorticoid and mineralocorticoid dose adjustments before intensive endurance exercise. Close symptomatic surveillance while adjusting adrenal replacement therapy before the event will likely result in less adverse side effects and improved performance (44). The guideline of the French Endocrine Society recommends an additional dose of 5 mg of HC every three hours, starting

Table 2. Medications used in the treatment of hyperkalemia (36,37)

Medicine	Dose	Effect duration	Side effect/complication
Dextrose/insulin	0.5-1 g/kg dextrose and 0.2 units of insulin for every 1 g of glucose	Fast	Hypoglycemia, hyperosmolarity
Salbutamol	Nebulized: 2.5 mg < 25 kg 5 mg > 25 kg	Fast	Tachycardia
Sodium bicarbonate	1-2 mmol/kg in 30-60 min	moderate	Sodium overload (hypertension)
Furosemide	1-2 mg/kg	moderate	Ototoxicity, nephrotoxicity
Ion exchange resins	p.o. or p.r. Calcium resonium 1 g/kg Sodium resonium 1 g/kg	Slow	p.o.: Nausea, constipation, paralytic ileus. If mixed with sorbitol, diarrhea p.r.: Cecal perforation
Ca-gluconate 10 %	0.5-1 mL/kg in 5-10 minutes		Hypercalcemia, tissue necrosis NOTE: Calcium gluconate antagonizes cardiac effects although does not have a potassium-lowering effect.

one hour before the activity, for long-duration, high-intensity activities (expert opinion) (45).

Other Drugs That Change Cortisol Metabolism

Some drugs, such as carbamazepine, phenytoin, phenobarbital, and rifampin, increase cortisol clearance by stimulating cytochrome p450 3A or P-glycoprotein efflux membrane transporters. Therefore, the use of these drugs with glucocorticoids may require the use of higher replacement doses, and if the necessary dose increase is not made, adrenal crisis may be induced (3,46,47).

Febrile and Non-febrile Illnesses

The most common triggers of adrenal crisis in children with AI are upper respiratory tract infections in young children and gastrointestinal infections in older children (3). Cortisol release increases 2-5 fold in febrile illnesses in children; whereas this increase is milder (2-3 fold) in cases of pharyngitis, urinary tract infection and otitis. It is more pronounced (about 5 fold) in cases of pneumonia, bacterial meningitis and fever of unknown origin. However, no relationship has been found between the degree of high fever and cortisol release (10). Various guidelines on the management of AI also recommend increasing the dose of HC during febrile periods of infection (3,20).

Severe Trauma or Illnesses Requiring Intensive Care

One study showed mean admission cortisol levels were elevated (35 ± 3 µg/dL) and declined significantly over the following 10 days in severely injured patients (48). In this study, cortisol levels did not correlate with injury severity. In another study, plasma cortisol was found to be elevated in proportion to the degree of disease in patients followed up in intensive care (49). Patients with normal hypothalamic-pituitary-adrenal axis function consistently exhibit elevated total serum cortisol levels up to 10 times the upper limit of normal during critical illness (50,51). A cross-sectional study reported that serum free cortisol, 24-hour urinary cortisol and cortisol metabolite levels were significantly higher in acute major trauma and sepsis compared with healthy controls (7). The International Endocrine Society guideline recommends the use of an adrenal crisis dose of HC (initially 50 mg/m^2 IV HC, then 50-100 mg/m^2/day, IV or IM HC at 6-hour intervals) in children and adolescents with AI in cases of severe trauma, labor and in conditions requiring intensive care (3).

Minor Local Procedures without Sedation or General Anesthesia

Dental extractions and local anaesthetic procedures can induce stress in subjects. Many studies in adults and children have shown that dental procedures, like local anaesthetic injections, dental restoration and extractions elevated the levels of salivary cortisol (52,53,54,55). It was observed that salivary cortisol measured after tooth extraction was approximately twice (but not more) that of control subjects (52,53). When the difference in the effect of one or two tooth extractions was analysed, no significant difference was found between salivary cortisol levels (56).

Imaging Procedures Under General Anesthesia

It has been reported that cortisol levels did not increase during general anesthesia in children without AI when anesthesia was used for imaging procedures, and that cortisol levels at the level of the stress response (≥550 nmol/L) were found in 23 % of patients on awakening and 52 % on recovery from anesthesia (8). No effect of age, duration of anesthesia and recovery time on the cortisol response was found. It was concluded that anesthesia alone did not stimulate the stress response in children with AI, but cortisol levels increased significantly during the recovery process. The highest increase in cortisol levels seen in the study was 4-fold compared with baseline (8). Another study found that in children without AI, anesthesia increased cortisol levels 3-4-fold, the lowest increase was in imaging

J Clin Res Pediatr Endocrinol
2025;17(Suppl 1):80-92

anesthesia (3-fold), and the depth of anesthesia did not affect the amount of cortisol increase (9).

Invasive Procedures Performed Under General Anesthesia

High-quality trials on perioperative steroid management in children with AI are lacking, and more research is needed to establish evidence-based clinical guidelines (15). The amount and timing of cortisol released from the adrenal cortex in response to surgery in individuals without AI is taken into account when determining the stress doses to be administered in the perioperative period in adult patients, and the dose is adjusted according to the level of surgical stress (57). However, the stress doses and application methods recommended to date are generally based on case series published before 2000 with a low level of evidence and small numbers of patients (6). According to the study published by Kehlet and Binder (58) in 1973, the estimated cortisol secretion in the first 24 hours due to surgical stress in healthy adults was 75-150 mg/day for major surgery and 50 mg/day for minor surgery. In older studies, cortisol secretion in the first 24 hours of major surgery generally does not exceed 200 mg/day (maximum 300 mg/day in one study) (11). To date, perioperative stress cortisol doses have been recommended based on this informations (59). As there is little data in children, adult doses are adapted to children.

A recent systematic review and meta-analysis evaluated 71 studies published between 1990-2016 that investigated the cortisol stress response induced by surgeries with different severity (excluding brain surgery) in adults without AI (6,60). In the trials conducted in patients undergoing minor surgery, no cortisol peak was observed during surgery, and cortisol levels within six hours after surgery did not increase significantly compared with baseline. However, the mean cortisol release in the first 24 hours after surgery was approximately doubled in this group compared to healthy, non-stressed individuals. Total serum cortisol was found to peak during the extubation period and between postoperative 6 and 18 hours for moderate and major surgery respectively. In addition, mean cortisol levels in these two groups remained higher than baseline for up to three days postoperatively (up to seven days in a smaller number of studies). Mean cortisol release in the first 24 hours after moderate and major surgery was 1.9 and 1.7 times higher compared to the minor surgery group, and 4 and 3.5 times higher compared to healthy and non-stressed people, respectively. In conclusion, the extent of surgery significantly influenced perioperative cortisol synthesis. Perioperative cortisol release was found to be higher in female patients compared with male patients, in open surgery compared with laparoscopic surgery, and in those who received general anesthesia compared with those who received regional (spinal/epidural) anesthesia (6).

In a recent case-control study (57), perioperative cortisol measurements were analysed in 93 adult patients (23 minor, 33 intermediate, 37 major/major + according to the severity of surgery) and it was found that serum cortisol peak and time to peak were positively correlated with the degree of surgical invasiveness. Cortisol peaks were observed at a median of 2 (0-21.5), 4 (0-19) and 8 (0-94) hours after induction of anesthesia in minor, intermediate and major/major + operations, respectively. Cortisol levels returned to baseline at a median of 8 hours and 2 (1-5) days after induction of anaesthesia in moderate and major/major + surgery, respectively. The authors suggested that the current recommendations for perioperative stress doses to achieve these levels are high and they can be reduced, and also they can be tapered to maintenance doses in a shorter time. However, this should be tested with prospective studies to show that it is safe and practically applicable (57).

Studies of the cortisol response to perioperative stress in children are very limited. In two studies investigated the effect of minor surgical procedures performed under general and epidural anesthesia, it was found that cortisol levels were 2.5-3 fold higher during perioperative process in the general anesthesia group but not epidural anesthesia group (61,62). Khilnani et al. (63) showed that postoperative cortisol levels in 98 children and young adults increased significantly. Age, duration of surgery and type of anesthesia were found to have no effect on cortisol levels. In another study, during follow up of 30 children (from preoperative period to one hour after the end of the surgery) who underwent minimally and moderately invasive urological surgery, it was found that cortisol levels peaked at one hour postoperatively. However, it was reported that mean serum cortisol levels did not increase significantly from baseline at any measurement (23). There was no difference in cortisol levels between age groups, general or caudal anesthesia and minimally or moderately invasive surgery. Based on this, it has been recommended that the perioperative glucocorticoid dose in minimally and moderately invasive urological surgery should not exceed three times the daily dose and that the dose increase should cover the postoperative period rather than the preoperative period.

Methods of perioperative administration of stress doses in adults were compared in a recent study (7). In first part of the study, postoperative serum cortisol levels were monitored in 22 patients (without AI) undergoing elective surgery (mostly moderately invasive). In the second part, ten patients with primary AI received 200 mg/day of HC by four different routes (oral, IM, IV or continuous IV infusion

of equal doses at 6-hour intervals) at 1-week intervals and serum cortisol levels were monitored 24 hours after the initiation of administration. Then data from these two part of studies were compared. The authors found that the mean cortisol concentrations observed in healthy volunteers during surgical stress could only be achieved by continuous infusion in patients with AI, and in the other application routes cortisol levels fell below these levels before the next dose. When pharmacokinetic modelling was performed, it was found that administration of 200 mg of HC via continuous IV infusion after a 50-100 mg HC bolus was the best way to achieve cortisol levels within the desired range. The authors recommended that continuous infusion of HC should be preferred for the prevention or treatment of adrenal crisis in high-stress situations (7). As most of the surgeries in the study were moderately invasive, it was noted that higher serum cortisol levels may be found in more invasive and longer surgeries. Chee et al. (64) criticised this study and suggested that adding information on blood pressure and intraoperative hemodynamic status to such a study could provide further physiological evidence when comparing treatment regimens.

In a systematic review of the need for perioperative glucocorticoids in adult patients on pharmacological doses of steroids for reasons other than AI, it was found that the use of steroids at the patients' daily dose did not lead to adrenal crisis in this patient group, without increasing the perioperative loading dose. In cases of postoperative hypotension, it was reported that there was often an explanation for this and that it resolved with volume repletion. The results of the preoperative ACTH stimulation test did not correlate with the postoperative clinical status of the patients. It has been suggested that perioperative glucocorticoid doses can be kept lower in this group of patients than in patients on glucocorticoids for PAI. However, further studies are needed in this area, as the sample size was small and the statistical power of the study was low (65).

Preferred Steroid Type

As HC also has a mineralocorticoid effect, the use of HC is preferred in situations of stress, especially in patients with mineralocorticoid deficiency. As 40-50 mg of HC can have a mineralocorticoid effect equivalent to 100 µg of fludrocortisone, the use of HC above this dose also meets the need for mineralocorticoid replacement. Prednisolone and methylprednisolone also have partial mineralocorticoid activity (66). As dexamethasone has no mineralocorticoid activity, it is not appropriate to use it alone in patients with mineralocorticoid deficiency (66). If necessary, it can be used in patients with secondary AI or isolated glucocorticoid deficiency. Otherwise, maintenance fludrocortisone should be given separately (3).

Good practice points:

1. Additional doses of steroids are not required for routine physical exercises (LIAs) (ungraded good practice statement).

2. Additional doses of steroids are not required for short-term (≤20 minutes) moderate and high-intensity exercises (ungraded good practice statement).

3. It would be appropriate to use additional doses of steroids during high-intensity excercise lasting longer than 30-60 minutes like marathon running, cycling race or etc (2⊕⊕OO).

4. It may be necessary to increase the HC replacement dose if a drug that increases cortisol metabolism or clearance is started (2⊕OOO).

5. Additional doses of steroids for mild, non-febrile illnesses are not required (2⊕OOO).

6. In febrile illnesses, the dose of oral HC used should be increased 2-3 times until the fever returns to normal. Infants and young children in particular should not be allowed to go hungry, and their fluid intake should be increased. For more serious infections, such as pneumonia or meningitis, the dose should be increased further (5 times) (1⊕⊕OO).

7. If there is diarrhea and/or vomiting, it is appropriate to give 3 times the current dose of oral HC (3-4 doses per day) until the condition improves (a few days). If diarrhea-vomiting persists, oral intake cannot be tolerated, there is severe weakness/impaired consciousness, and/or suspicion of adrenal crisis, 25, 50 and 100 mg HC or equivalent methylprednisolone should be administered IM to the patients < 3 years, 3-12 years and > 12 years, respectively (or 50-100 mg/m^2 for all ages) (or 2 mg/kg at all ages). Afterwards a healthcare provider should be consulted for IV fluid support (2⊕OOO).

8. In severe trauma or illnesses requiring intensive care, parenteral HC administration at adrenal crisis doses is appropriate until stability is achieved (1⊕⊕OO).

9. For minor dental procedures carried out under local anaesthetic, double the daily dose and return to the normal dose the following day (2⊕⊕OO).

10. For imaging procedures under general anesthesia, the HC dose should be increased (3-4 times), especially during waking and recovery from anesthesia. The normal dose should be resumed the following day (1⊕⊕⊕O).

11. Prior to colonoscopy under general anesthesia HC 50 mg/m^2/day IV/IM is used on the day of bowel evacuation. HC 50 mg/m^2/dose IV/IM is given before the procedure (2⊕OOO).

12. For invasive procedures performed under general anesthesia, increase the dose of HC (parenteral) for an appropriate period of time according to the degree of invasiveness of the surgery to be performed (1⊕⊕OO) (Table 3). Perioperative follow-up of these patients should preferably be carried out in a centre with a paediatric endocrinologist (2⊕OOO).

13. Stress doses should be given as HC, especially in patients with mineralocorticoid deficiency, and if HC cannot be given, equivalent doses of prednisolone (1/4 dose) or methylprednisolone (1/5 dose) is preferred (1⊕⊕OO).

Family Education

Several studies have shown that a significant proportion of patients with AI do not have sufficient information about personal management of the disease, do not carry a disease identification card or similar, or perform incorrect practices in stressful situations (3,18,45). So it has been suggested that continuous and effective education is needed. A Canadian study (1998-2007) found that only 47% of children with AI received a glucocorticoid dose increase prior to emergency admission (67). In a study analysing emergency admissions of children diagnosed with congenital adrenal hyperplasia (CAH) to three endocrine centres in Australia (2000-2015), it was found that 64% of patients received stress doses (22.1% IM), and this rate was lowest in the age group below 12 months (51.9%) (68).

The most important way to protect patients from life-threatening adrenal crisis is to constitute patient/family awareness through appropriate education (2,17). Informing patients and their families about the diagnosis and treatment of the child, stress states, symptoms of AI and increasing the dose of steroids in stress situations may improve management of the disease and reduce the frequency of adrenal crisis (45). They should also be trained in the use of IM HC in case of situations of severe stress, continuous vomiting or recognising symptoms of adrenal crisis, like an altered state of conscious. In a study conducted in the Netherlands, 246 patients receiving glucocorticoids for AI were trained in glucocorticoid treatment, dose increase in stress situations, and IM HC injection, and a questionnaire was administered before and six months after training. After the training, it was found that patients' correct answers to questions about managing stress situations increased significantly, and more patients started to carry informative materials about AI (18).

It is appropriate for patients to have a written document or identification bracelet/necklace to be shown to the first consulted healthcare professional regarding what should be done in emergency situations. IM or subcutaneous (SC) administration of HC in home settings may be life-saving when symptoms of adrenal crisis are felt or when oral HC cannot be taken due to vomiting. It may prevent the patient from deteriorating until he/she goes to a health institution. In a prospective study conducted in adults, Hahner et al. (69) showed that almost every patient carried an emergency card, but only 30% of the patients had a HC administration kit. In this study, it was highlighted that the rate of having an emergency injection kit was higher in people who had experienced adrenal crisis.

Many international and national guidelines recommend that all patients with AI (and/or their families) should be informed about the following topics: 1) diagnosis and routine medication doses; 2) stressful situations, symptoms of adrenal crisis and strategies to prevent adrenal crisis; and 3) to have an emergency glucocorticoid injection kit (HC hemisuccinate IM/IV ampoules, injector) and know how to use it (IM or SC injection) (3,13,20). Besides the IV/IM preparations containing HC, which are available in Turkey, auto-injectors containing ready-to-use HC are also available, in order to shorten the preparations for injection and prevent errors in application and are more widely used globally. The use of rectal HC suppositories is not recommended in cases of stress in patients with AI (70).

In order to provide a standardised approach in the prevention and treatment of adrenal crisis in children with AI in Turkey, the 'Emergency Treatment Plan for Patients Using HC Due to AI' (71) and the 'Perioperative Approach in Adrenal Diseases' protocol (72) were published by the Pediatric Endocrinology and Diabetes Association (CEDD). 'Patient identification cards' have been printed to be carried by patients diagnosed with CAH. The QR code on the card can be scanned to access the adrenal crisis management protocol available on the association's website. The cards also contain the patient's name and surname, the patient's family, the hospital where the patient is normally being treated and the doctor's contact details. In the guidelines of the French Society of Endocrinology, the framework of the educational programme that can be applied to patients diagnosed with AI has been presented (45).

In clinical practice, it is often observed that, even when patients receive education by written materials, some of the information is forgotten during follow-up. Therefore, it is

Table 3. Recommendations for the perioperative stress dose of glucocorticoids in children with adrenal insufficiency (3,20,72)

Surgical stress	Recommended HC dosage
Minor surgery (minimally invasive) - Examinations under anesthesia - Excision of skin lesions - Ear tube insertion - Cystoscopy - Circumcision - Bronchoscopy - Endoscopy, colonoscopy - Diagnostic laparoscopy - Inguinal hernia repair - Tonsillectomy	- HC 25 mg/m^2/dose is given intravenously before the procedure. When oral feeding is initiated after the procedure, HC is given at twice the normal dose, and the normal dose is continued the next day. OR - 50 mg/m^2/day or 2-3 times the HC replacement dose (first day) IM/IV.
Moderate surgery (moderately-significantly invasive) - Thyroidectomy - Ovarian cystectomy - Cholecystectomy - Hysterectomy - Nephrectomy - Major laparoscopic procedures - Gastrointestinal resections (segmental)	- 25-50 mg/m^2/dose of HC is given intravenously as a bolus before surgery. - Subsequently, 50-75 mg/m^2/day HC is administered as a continuous intravenous infusion or IV injection every 6 hours (the first one during surgery). - In uncomplicated cases, once the patient is stable, the dose is tapered by 25% per day within a few days to the previous maintenance dose. OR - HC 2 mg/kg is given as an IV infusion over 6 hours (or IM/SC every 6-8 hours) and the same dose is repeated until oral feeding is initiated. When oral feeding is initiated, HC is given orally at twice the daily dose and the dose is tapered back to the previous maintenance dose in 1-2 days.
Major surgery (severe invasive) - Cardiothoracic surgery - Intracranial surgery - Major oropharyngeal surgery - Major vascular, skeletal or neurological repairs - Major orthopedic spinal reconstruction - Major gastrointestinal reconstruction - Liver resection - Major genitourinary surgery - Multiple dental procedures under general anesthesia	- 50-100 mg/m^2/dose of HC is given intravenously as a bolus before surgery. - Subsequently, 100 mg/m^2/day of HC is given as a continuous intravenous infusion or intravenous injection every 6 hours (the first during surgery). - In uncomplicated cases, once the patient is stable, the dose is tapered by 25% per day and the previous maintenance dose is restored within a few days. OR - HC 2 mg/kg is given as an IV infusion over 6 hours (or IM/SC every 6-8 hours) and the same dose is repeated until oral feeding is initiated. When oral feedig is initiated, HC is given orally 3 times daily, and the dose is tapered back to the previous maintenance dose in 3-4 days.

*In patients with mineralocorticoid deficiency, fludrocortisone should be given preoperatively with a little amount of water if the calculated daily total HC is < 40 mg.
HC: hydrocortisone, IV: intravenous, IM: intramuscular, SC: subcutaneous

important to repeat training periodically (69,73,74,75). The precautions and rules to be taken during periods of illness should be repeated at each outpatient clinic follow-up and IM injections should be demonstrated.

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (76).

Good practice points:

1. In order to prevent adrenal crisis, all patients and/or their families should be educated about the conditions that trigger adrenal crisis, how to increase HC doses during illness, fever and other stressors. This education should also include, how to recognise signs of impending adrenal crisis, and what to do in this situation (ungraded good practice statement).

2. All patients should be encouraged to carry a card/information sheet/medical alert bracelet or necklace indicating the diagnosis of AI and need for HC administration (ungraded good practice statement).

3. All patients should have a glucocorticoid injection kit (100 mg HC hemisuccinate ampoule, syringe with needle) and be trained for self injection (SC or IM injection) in emergency situations (ungraded good practice statement).

Footnotes

Authorship Contributions

Concept: Emine Çamtosun, Özlem Sangün, Design: Emine Çamtosun, Özlem Sangün, Literature Search: Emine Çamtosun, Özlem Sangün, Writing: Emine Çamtosun, Özlem Sangün.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hahner S. Acute adrenal crisis and mortality in adrenal insufficiency: Still a concern in 2018! Ann Endocrinol (Paris). 2018;79:164-166. Epub 2018 Apr 30.
2. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Ventz M, Quinkler M, Allolio B. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010;162:597-602. Epub 2009 Dec 2.
3. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:364-389. Epub 2016 Jan 13.
4. Miller BS, Spencer SP, Geffner ME, Gourgari E, Lahoti A, Kamboj MK, Stanley TL, Uli NK, Wicklow BA, Sarafoglou K. Emergency management of adrenal insufficiency in children: advocating for treatment options in outpatient and field settings. J Investig Med. 2020;68:16-25. Epub 2019 Feb 28.
5. Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal crisis: still a deadly event in the 21st century. Am J Med. 2016;129:339. Epub 2015 Sep 9.
6. Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, Foster MA, Lord JM, Karavitaki N, Wass JA, Murad MH, Arlt W, Bancos I. The cortisol stress response induced by surgery: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018;89:554-567. Epub 2018 Aug 23.
7. 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;105:2262–2274.
8. Rains PC, Rampersad N, De Lima J, Murrell D, Kinchington D, Lee JW, Maguire AM, Donaghue KC. Cortisol response to general anesthesia for medical imaging in children. Clin Endocrinol (Oxf). 2009;71:834-839. Epub 2009 Mar 28.
9. Hsu AA, von Elten K, Chan D, Flynn T, Walker K, Barnhill J, Naun C, Pedersen AM, Ponaman M, Fredericks GJ, Crudo DF, Pinsker JE. Characterization of the cortisol stress response to sedation and anesthesia in children. J Clin Endocrinol Metab. 2012;97:E1830-E1835. Epub 2012 Aug 1.
10. Nickels DA, Moore DC. Serum cortisol responses in febrile children. Pediatr Infect Dis J. 1989;8:16-20.
11. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg. 1994;219:416-425.
12. 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. Anesthesia. 2020;75:654-663. Epub 2020 Feb 3.
13. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:4043-4088.
14. Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management: approaches based on current evidence. Anesthesiology. 2017;127:166-172.
15. Heath C, Siafarikas A, Sommerfield A, von Ungern-Sternberg BS. Peri-operative steroid management in the paediatric population. Acta Anaesthesiol Scand. 2021;65:1187-1194. Epub 2021 Aug 4.
16. Freudzon L. Perioperative steroid therapy: where's the evidence? Curr Opin Anaesthesiol. 2018;31:39-42.
17. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361:1881-1893.
18. Repping-Wuts HJ, Stikkelbroeck NM, Noordzij A, Kerstens M, Hermus AR. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. Eur J Endocrinol. 2013;169:17-22.
19. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015;172:R115-R124. Epub 2014 Oct 6.
20. Reznik Y, Barat P, Bertherat J, Bouvattier C, Castinetti F, Chabre O, Chanson P, Cortet C, Delemer B, Goichot B, Gruson D, Guignat L, Proust-Lemoine E, Sanson MR, Reynaud R, Boustani DS, Simon D, Tabarin A, Zenaty D. SFE/SFEDP adrenal insufficiency French consensus: Introduction and handbook. Ann Endocrinol (Paris). 2018;79:1-22. Epub 2018 Jan 12.
21. 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;71:586-594. Epub 2021 Mar 4.
22. Nisticò D, Bossini B, Benvenuto S, Pellegrin MC, Tornese G. Pediatric adrenal insufficiency: challenges and solutions. Ther Clin Risk Manag. 2022;18:47-60.
23. Taylor LK, Auchus RJ, Baskin LS, Miller WL. Cortisol response to operative stress with anesthesia in healthy children. J Clin Endocrinol Metab. 2013;98(9):3687-3693. Epub 2013 Jul 16.
24. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21:55-89.
25. 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;43:91-159.
26. Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting AL, Kasperlik-Zaluska A, Kämpe O, Løvås K, Meyer G, Pearce SH. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275:104-115. Epub 2013 Dec 16.
27. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. J Pediatr. 1990;117:892-896.
28. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab. 1991;72:39-45.
29. Stewart PM and Newell-Price JDC. The adrenal cortex. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, (eds). Williams Textbook of Endocrinology, 13th ed. Philadelphia, PA: Saunders; 2016: Chapter 15
30. Patti G, Guzzeti C, Di Iorgi N, Maria Allegri AE, Napoli F, Loche S, Maghnie M. Central adrenal insufficiency in children and adolescents. Best Pract Res Clin Endocrinol Metab. 2018;32:425-444. Epub 2018 Apr 10.

31. Rushworth RL, Torpy DJ, Falhammar H. Adrenal crisis. N Engl J Med. 2019;381:852-861.

32. Greenbaum LA. Fluid and Electrolyte Disorders. In Kliegman MR, St Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, Behrman RE (eds). Nelson Textbook of Pediatrics (21th Ed) Elsevier, Philedelphia 2019; pg 392-432.

33. Anigilaje EA. Management of diarrhoeal dehydration in childhood: a review for clinicians in developing countries. Front Pediatr. 2018;6:28.

34. Chanson P, Guignat L, Goichot B, Chabre O, Boustani DS, Reynaud R, Simon D, Tabarin A, Gruson D, Reznik Y, Raffin Sanson ML. Group 2: Adrenal insufficiency: screening methods and confirmation of diagnosis. Ann Endocrinol (Paris). 2017;78:495-511. Epub 2017 Nov 23.

35. Kirkgoz T, Guran T. Primary adrenal insufficiency in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2018;32:397-424. Epub 2018 Jun 6.

36. Masilamani K, van der Voort J. The management of acute hyperkalaemia in neonates and children. Arch Dis Child. 2012;97:376-380. Epub 2011 Sep 13.

37. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. Pediatr Nephrol. 2011;26:377-384. Epub 2010 Dec 22.

38. Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, Gidding SS, Isabel-Jones J, Kavey RE, Marx GR, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation. 1994;90:2166-2179.

39. Measuring Physical Activity Intensity. Last Accessed Date: 25.12.2024. Available from: https://www.cdc.gov/physicalactivity/basics/measuring/index.html

40. Weise M, Drinkard B, Mehlinger SL, Holzer SM, Eisenhofer G, Charmandari E, Chrousos GP, Merke DP. Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. J Clin Endocrinol Metab. 2004;89:3679-3684.

41. Simunkova K, Jovanovic N, Rostrup E, Methlie P, Øksnes M, Nilsen RM, Hennø H, Tilseth M, Godang K, Kovac A, Løvås K, Husebye ES. Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure. Eur J Endocrinol. 2016;174:97-105. Epub 2015 Oct 22.

42. Bachi AL, Rios FJ, Vaisberg PH, Martins M, de Sá MC, Victorino AB, Foster R, Sierra AP, Kiss MA, Vaisberg M. Neuro-immuno-endocrine modulation in marathon runners. Neuroimmunomodulation. 2015;22:196-202. Epub 2014 Aug 27.

43. Brooks K, Carter J. Overtraining, exercise, and adrenal insufficiency. J Nov Physiother. 2013;3:11717.

44. Bonnecaze AK, Reynolds P, Burns CA. Stress-dosed glucocorticoids and mineralocorticoids before intensive endurance exercise in primary adrenal insufficiency. Clin J Sport Med. 2019;29:e73-e75.

45. Guignat L, Proust-Lemoine E, Reznik Y, Zenaty D. Group 6. Modalities and frequency of monitoring of patients with adrenal insufficiency. Patient education. Ann Endocrinol (Paris). 2017;78:544-558. Epub 2017 Dec 1.

46. Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. Br Med J (Clin Res Ed). 1986;292:1185-1186.

47. UpToDate®. https://www.uptodate.com/contents/image/print?imageKey = RHEUM%2F53228

48. Offner PJ, Moore EE, Ciesla D. The adrenal response after severe trauma. Am J Surg. 2002;184:649-653.

49. Wade CE, Lindberg JS, Cockrell JL, Lamiell JM, Hunt MM, Ducey J, Jurney TH. Upon-admission adrenal steroidogenesis is adapted to the degree of illness in intensive care unit patients. J Clin Endocrinol Metab. 1988;67:223-227.

50. Harris MJ, Baker RT, McRoberts JW, Mohler JL. The adrenal response to trauma, operation and cosyntropin stimulation. Surg Gynecol Obstet. 1990;170:513-516.

51. Jarek MJ, Legare EJ, McDermott MT, Merenich JA, Kollef MH. Endocrine profiles for outcome prediction from the intensive care unit. Crit Care Med. 1993;21:543-550.

52. Gadicherla S, Shenoy RP, Patel B, Ray M, Naik B, Pentapati KC. Estimation of salivary cortisol among subjects undergoing dental extraction. J Clin Exp Dent. 2018;10:e116-e119.

53. Umeanuka OT, Saheeb BD, Uguru CC, Chukwuneke FN. Evaluation of cortisol concentrations in saliva as a measure of stress in patients having routine dental extractions. Br J Oral Maxillofac Surg. 2015;53:557-560. Epub 2015 Apr 14.

54. Kandemir S, Okşan T, Alpöz AR, Ergezer G, Kabalak T. Salivary cortisol levels in children during dental treatment. J Marmara Univ Dent Fac. 1997;2:639-642.

55. Akyuz S, Pince S, Hekin N. Children's stress during a restorative dental treatment: assessment using salivary cortisol measurements. J Clin Pediatr Dent. 1996;20:219-223.

56. Umeanuka OT, Saheeb BD, Chukwuneke FN, Uguru CC. A comparative analysis of the level of cortisol and the number of teeth extracted among patients undergoing routine dental extraction. Niger J Clin Pract. 2016;19:700-703.

57. Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, Williams EL, Moorthy K, Tolley N, Jiao LR, Spalding D, Palazzo F, Meeran K, Tan T. Redefining the stress cortisol response to surgery. Clin Endocrinol (Oxf). 2017;87:451-458. Epub 2017 Aug 30.

58. Kehlet H, Binder C. Value of an ACTH test in assessing hypothalamic-pituitary-adrenocortical function in glucocorticoid-treated patients. Br Med J. 1973;2:147-149.

59. Seo KH. Perioperative glucocorticoid management based on current evidence. Anesth Pain Med (Seoul). 2021;16:8-15. Epub 2021 Jan 15.

60. Donati A, Ruzzi M, Adrario E, Pelaia P, Coluzzi F, Gabbanelli V, Pietropaoli P. A new and feasible model for predicting operative risk. Br J Anaesth. 2004;93:393-399. Epub 2004 Jun 25.

61. Boninsegni R, Salerno R, Giannotti P, Andreuccetti T, Busoni P, Santoro S, Forti G. Effects of surgery and epidural or general anesthesia on testosterone, 17-hydroxyprogesterone and cortisol plasma levels in prepubertal boys. J Steroid Biochem. 1983;19:1783-1787.

62. Salerno R, Forti G, Busoni P, Casadio C. Effects of surgery and general or epidural anesthesia on plasma levels of cortisol, growth hormone and prolactin in infants under one year of age. J Endocrinol Invest. 1989;12:617-621.

63. Khilnani P, Munoz R, Salem M, Gelb C, Todres ID, Chernow B. Hormonal responses to surgical stress in children. J Pediatr Surg. 1993;28:1-4.

64. Chee YJ, Dinesh M, Lim SC. Letter to the Editor: "Prevention of adrenal crisis: cortisol responses to major stress compared to stress dose hydrocortisone delivery". J Clin Endocrinol Metab. 2021;106:e395-e396.

65. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Arch Surg. 2008;143:1222-1226.

66. Hughes CR, Man E., Achermann J. Adreal cortex and its disorders.In: Dattani MT, Brook CG, eds. Brook's Clinical Pediatric Endocrinology 7th edition, Hoboken NJ:Wiley-Blackwell; 2020:335-407.

67. Leblicq C, Rottembourg D, Deladoëy J, Van Vliet G, Deal C. Are guidelines for glucocorticoid coverage in adrenal insufficiency currently followed? J Pediatr. 2011;158:492-498. Epub 2010 Oct 30.

68. Chrisp GL, Maguire AM, Quartararo M, Falhammar H, King BR, Munns CF, Torpy DJ, Hameed S, Rushworth RL. Variations in the management of acute illness in children with congenital adrenal hyperplasia: An audit of three paediatric hospitals. Clin Endocrinol (Oxf). 2018;89:577-585. Epub 2018 Sep 24.

69. Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M, Allolio B. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015;100:407-416. Epub 2014 Nov 24.

70. De Vroede M, Beukering R, Spit M, Jansen M. Rectal hydrocortisone during stress in patients with adrenal insufficiency. Arch Dis Child. 1998;78:544-547.

71. Abacı A. Adrenal yetmezlik nedeni ile hidrokortizon kullanan hastalar için acil durum tedavi planı. Available from: https://cocukendokrindiyabet.org/wp-content/uploads/adrenal-yetmezlik-nedeni-ile-hidrokortizon-kullanan-hastalar-icin-acil-durum-tedavi-plani.pdf

72. Abacı A. Adrenal hastalıklarda perioperatif yaklaşım. Available from: https://cocukendokrindiyabet.org/wp-content/uploads/adrenal-hastalarda-perioperatif-yaklasim.pdf

73. Harsch IA, Schuller A, Hahn EG, Hensen J. Cortisone replacement therapy in endocrine disorders - quality of self-care. J Eval Clin Pract. 2010;16:492-498. Epub 2010 Feb 22.

74. Fleming LK, Rapp CG, Sloane R. Caregiver knowledge and self-confidence of stress dosing of hydrocortisone in children with congenital adrenal hyperplasia. J Pediatr Nurs. 2011;26:e55-e60. Epub 2011 May 11.

75. Braatvedt GD, Newrick PG, Corrall RJ. Patients' self administration of hydrocortisone. BMJ. 1990;301:1312.

76. Odabaşı Güneş S, Peltek Kendirci HN, Ünal E, Buluş AD, Dündar İ, Şıklar Z. Clinical, biochemical and molecular characteristics of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Res Pediatr Endocrinol. 2025;17(Suppl 1):3-11.