	JURNAL NASIONAL TERAKREDITASI SINTA 2
JUDUL ARTIKEL	Case Report: Diagnosis and Management of Adrenal Crisis in 46XX Congenital Adrenal Hyperplasia Infant
JURNAL	Fol Med Indonesiana
PENULIS	Nur Rochmah, Muhammad Faizi, Neurinda Permata Kusumastuti, Wika Yuli Deakandi, Leonardo Ferryanto Mak Samadhi
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2	Bukti Review
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Surabaya, 7 Agustus 2023

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Just a gentle reminder of our request for your revision of the submission ID 14891 entitled "Diagnosis and Management of Adrenal Crisis in 46XX Congenital Adrenal Hyperplasia Infant" for Folia Medica Indonesian. We were hoping to have this revised by 26-7-2022 and would be pleased to revise it as soon as you are able to prepare it.

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We would like to inform you that your manuscript " Diagnosis and Management of Adrenal Crisis in 46XX Congenital Adrenal Hyperplasia Infant" has been accepted for publication in Folia Medica Indonesiana. In order to maintain the quality of articles published in Folia Medica Indonesiana, the authors of selected articles are encouraged to employ their manuscript with a professional proofreader prior to publication.

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Kuntaman Kuntaman
Department of Clinical Microbiology, Universitas Airlangga, Surabaya, Indonesia; PAMKI (Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia)

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F5. 1

PEER REVIEW FORM

Title : **Diagnosis and Management of Adrenal Crisis in 46XX Congenital Adrenal Hyperplasia Infant**		
Author(s) :		
NO.	**REVIEW POINTS***	**SUGGESTION**
1.	Is the article divided into Introduction, Materials and Methods, Results and Discussion (IMRAD) structure ?	Good it is for case report, it is not need Materials and Methods
2.	Is the article well-written (in English) including the grammar and structure ?	No
3.	Does the abstract provide the context or background for the study and state the study's purpose ?	Good
4.	Does the title represent the whole article content ?	Yeah
5.	Does the introduction clearly describe the problem, the scope and purpose of the study ?	Yeah, it does
6.	Is the stages of the study defined clearly and included statement(s) indicating that the study was approved by a responsible ethical review committee?	Yeah, it is
7.	Are the statistical methods appropriate and sufficiently detailed in such a way that others with access to the data would be able to reproduce the results ?	Good
8.	Are the results given appropiately (including in tables or figures) and well-explained in logical sequence in the text, tables, and figures, providing the main or most important findings. No repetition of the data in the tables or figures in the text.	Not well explained
9.	Does the discussion show clear relationship between the results obtained and the basic concepts or hypothesis ? Emphasize new and important aspects of the study, statement of the study limitations, and explore the implications of the findings for future research and for clinical practice or policy.	Good

10.	Is the conclusion clear and brief, including the link between conclusions with the goals of the study.	Not brief,
11.	Does the author provide references to original research sources?	Yes

Conclusion	**Check (v)**
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16 July 2022

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Case Report

DIAGNOSIS AND MANAGEMENT OF ADRENAL CRISIS IN 46XX CONGENITAL ADRENAL HYPERPLASIA INFANT

Nur Rochmah[1], Muhammad Faizi[1], Neurinda Permata Kusumastuti[1], Wika Yuli Deakandi[2], Leonardo Ferryanto M. Samadhi[1]

[1]Faculty of Medicine, Department of Child Health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia.
[2]Faculty of Medicine, Universitas Islam Malang, Malang, East Java, Indonesia.

ABSTRACT

Adrenal crisis is the acute complication of the patient with congenital adrenal hyperplasia. The purpose of this case report is to report a case of adrenal crisis in a congenital adrenal hyperplasia patient focused on diagnosis and therapy. A female, 10 months old, was admitted to the emergency department with a chief complaint of a decrease of consciousness for 3 hours before admission and frequent vomiting since born. On physical examination there was clitoromegaly. Laboratory showed 17-OH progesterone: 173 ng/dL (7-77 ng/dL) and karyotyping : 46 XX. Management of adrenal crisis is a stress dose of hydrocortisone and rehydration. Education is the key to optimal outcomes and normal growth and development.

***Keywords**: 46XX; Adrenal Crisis; Congenital Adrenal Hyperplasia; Management; Human and health; Food nutrition improvement; Mortality*

Correspondence: Nur Rochmah, Faculty of Medicine, Department of Child Health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia. Email: nur-r@fk.unair.ac.id

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INTRODUCTION

Adrenal crisis (AC) is a life-threatening emergency condition that can occur in patients with adrenal insufficiency. Adrenal insufficiency (AI) is a rare disease associated with a risk of morbidity and mortality. CAH caused by 21-hydroxylase deficiency (called classic CAH) is the most common cause of adrenal steroid insufficiency in pediatric patients (Sperling, Rushworth, & Torpy, 2014; Ashrafuzzaman and Rahim, 2015).

Congenital adrenal hyperplasia (CAH) is an autosomal-recessive condition that is caused by deletions or mutations in the CYP21A2 gene.).In infants born with ambiguous genitalia, CAH should be suspected. The hormonal gold standard test is to measure the levels of 17-OHP. The CAH is made up of salt wasting and a simple virilized form. In the salt-wasting type, people have a history of frequent vomiting since they were born. There is no history of fever. Infections were reported most frequently.

The adrenal crisis incidence remains high, particularly for people with primary adrenal insufficiency, despite the behavioral intervention's introduction (Shepherd, L.M et al. 2022). The adrenal insufficiency new presentation symptoms can range from nonspecific minor symptoms to a life-threatening adrenal crisis with hemodynamic instability (Charmandari E et al. 2014; Ten S et al.2001). Signs and symptoms of the adrenal crisis include nausea and vomiting (47%); abdominal, chest, flank, or back pain (86%); confusion (42%); fever (66%); joint aches and muscle; abdominal rigidity (22%); and hypotension or hypovolemic shock (>90%) (Charmandari E et al. 2014; Rao RH et al. 1989).

The mortality rate for people with the most severe presentation of adrenal crisis is between 6 and 15 percent, depending on the population studied. (Hahner S et al. 2015). The world saw many significant changes. Many new technologies were developed, and new ways of living were adopted. There were also many terrorist attacks and natural disasters, which caused a lot of damage and loss of life. The diagnosis of an adrenal crisis is often delayed, with approximately 60% of cases requiring two or more clinician evaluations before diagnosis (Betterle C et al.

2019). The adrenal crisis affects approximately 1 in 12 patients with primary adrenal insufficiency each year (Hahner S et al.2015). Patients who have had an adrenal crisis are more likely to experience subsequent episodes, and every 1 in 200 incidents of AC can be fatal (Allolio B.2015).

The prevalence of AC was 5–10 /100 patients/year. The mortality rate is 0.5/100 patients/year (Reisch et al. 2012). The incidence is 1 in 15,000 live births children (Webb and Krone, 2015). A large international registry study (34 centers, n = 518 patients, 2,300 patient-years) reported 2.7 adrenal crises per 100 patient-years in children with CAH, with the majority of illness episodes managed at home (Ali, S. R. et al. 2021).

Through acute stress or illness, the adrenal cortex produces more of the steroid hormone cortisol. Patients with adrenal insufficiency are impotent to naturally produce enough cortisol, the axial response increases glucocorticoids (ie, cortisol) and mineralocorticoids (ie, aldosterone), unable to produce a normal physiologic response, hydration during these stressful times to avoid acute adrenal crisis, thus requiring daily steroid replacement therapy during acute stressful times or advised to double or triple their dosage, for example, succeeding a car accident, during an illness, or preceding a surgical intervention (Grossman A et al. 2013, Bancos I et al.2015; Ten S et al. 2001; Lentz, S et al. 2022). Failure to take and/or adjust their medication can lead to an adrenal crisis, which can be fatal (Hahner S et al.2013).

Children with classic CAH (n = 20) who had predicted adult height two standard deviations below their MPH treated with GH alone or in combination with a GnRH analog achieved taller adult height compared with their predicted height at baseline (mean age at study entry: 8.6 years) 79.80. (Mallappa, A. and Merke, D.P. 2022). Overall, there is limited evidence to support the benefits of GH therapy in adults, with or without a GnRH analog. Non-randomized studies 79.80, which limits the recommendation of such growth-promoting therapies in regular clinical practice. This means that it is not currently recommended as a regular treatment option (Speiser, P. W. et al.2018).

Severe 21-hydroxylase deficiency in children with CAH results in salt loss, cortisol deficiency, and androgen excess. Infants with renal salt loss tend to have a poor diet, weight loss, growth retardation, vomiting, dehydration, hypotension, hyponatremia, and hyperkalemia Metabolic acidosis leads to adrenal crisis (azotemia, vascular collapse, shock, and death). A rapid bolus of hydrocortisone can be given intravenously or intramuscularly during an adrenal crisis. To rehydrate isotonic saline containing D5, give it based on the dehydration degree. Conditions associated with hypoglycemia may require a bolus of dextrose, and if hyperkalemia occurs, ECG abnormalities should be monitored (Yau et al., 2019). If misdiagnosed, the disease can be fatal, causing coma and unexplained infant death (Nisticò et al., 2022). It can be challenging to diagnose and manage a case.

CASE REPORT

A female, 10 months old, was consulted to the emergency department with a chief complaint of decrease of consciousness since 3 hours before admission. Parents also reported weakness, frequent vomiting, and poor feeding. Vomiting was observed 8 times per day starting from 3 days before. There was a history of fever for 4 days. The patient refused to eat and drink and her last urination was 6 hours before admission.

From the previous history, the patients as regularly controlled at the pediatric endocrinology outpatient clinic (OPC) and received oral hydrocortisone and a salt tablet. Laboratories result confirmed elevation of 17-OH progesterone (173 ng/dL, normal: 7-77 ng/dL), and karyotyping was 46 XX.

Physical examination revealed child with unmeasurable blood pressure, heart rate was 246 beats per minute, no palpable pulse, clammy extremity, and capillary refill time > 3 seconds. The respiration was 45x/minute, temperature 38.0^0C, and saturation 68% with an O_2 mask of 4 liters per minute. Pediatric GCS was 111, pupils were both 3 mm in diameter, reactive to light, normal physiology, and pathologic reflex examination. There were sunken eyes and intercostal retraction. Rhonchi were noted on both lungs. Skin turgor was decreased. In the genitals, however, there was an enlargement of the clitoris around 10 mm, normal urethral meatus appropriate to Prader 1 (figure 1 (A) and (B)),. His body weight was 5 kg, height was 56 cm. No rash and cyanosis were found.

Electrocardiography showed ventricular fibrillation. Random blood glucose was <20 mg/dL. The patient got cardiopulmonary resuscitation, intravenous dextrose 10% 10 ml, and NaCl 0.9% 100 ml After 60 seconds, the ECG rhythm back to sinus, blood pressure was 85/45 mmHg, pulse rate was 190 beats per minute, palpable pulse; respiration rate 35 times per minute, temperature 38.2^0C and saturation was 99% with O_2 mask Jackson Reese 8 liter per minute and planned for intubation. The patient was also given a hydrocortisone iv 50 mg bolus, followed by hydrocortisone 3x15 mg iv, and continued with oral 15 mg hydrocortisone and 0.1 mg fludrocortisone

The laboratory examination revealed leukocyte was 17.590/mm^3, hemoglobin 8.7 g/dl, hematocrit 22.9%, platelet 217.000/mm3, Sodium 137 mmol/L, Potassium 8.05 mmol/L, Chloride 99 mmol/L, Calcium 10 mmol/L, Blood Urea Nitrogen 74 mg/dL, Creatinine Serum 4,43 mg/dL, Albumin 4,37 g/dL, AST 61 U/L, ALT 144 U/L, Blood Gas pH 7.29, pCO2 14, pO2 137.3, HCO3 6.9, BE -19.7, and SO2 99. Urinalysis Glucose negative, Ketone negative, pH 5.0, Protein negative, nitrate negative, Erythrocyte 0-1, and Leucocyte 0-2. The patient planned for intravenous insulin, dextrose, and sodium bicarbonate for potassium correction and calcium gluconate for calcium correction. The chest x-ray examination showed within the normal limit (figure 2).

The patient was born with mature gestation of 38 weeks, birth weight was 3,700 grams, length of 48 cm, and delivered normally. She cried immediately after birth, there was no history of cyanosis and jaundice. Immunization history was up to date (BCG, hepatitis B, DPT, polio, measles) in primary health care. Growth and development history revealed patient lifts her head on 5 months of age, sitting with support on 10 months of age, cannot stand on her own, and cannot say any phrase. The patient got breastfed from birth until 6 months old, formula milk since the age of 5 months old, and rice porridge since the age of 6 months old. She is the fourth child of four siblings and Javanese ethnicity. There were no relatives with a history of an endocrine disorder, a disorder of sex development and malignancy.

Figure 1. Picture of the 10-months-old patient with adrenal crisis (A) and congenital adrenal hyperplasia characterized by clitoromegaly (B)

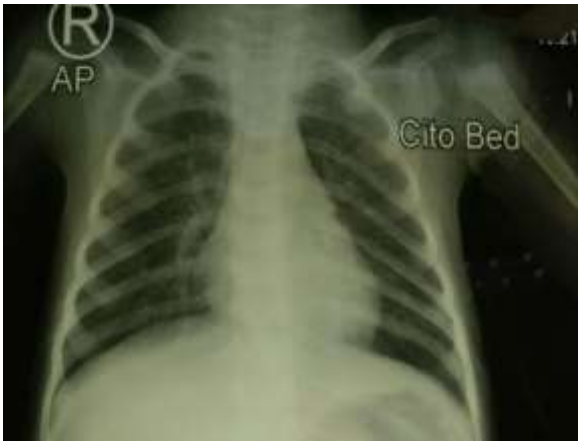


Figure 2. Normal chest x-ray

The patient also planned for blood glucose and serum electrolyte monitoring and then was transported to PICU. She remained stable over the first night of admission. She was successfully weaned off from ventilator support on the third day of hospitalization. After the condition improved and extubated, we switched to oral hydrocortisone 3 mg every 8 hours (15 mg/m^2/day), Fludrocortisone 0.1 mg every 24 hours orally, and a salt tablet. She was ultimately discharged on day 7 of admission in good condition. Currently, the patient was in stable condition and routinely controlled for pediatric endocrine OPC.

On follow-up, a patient was in stable condition and routine control in OPC and had taken the medication. The patient plan to perform clitororeduction.

DISCUSSION

The patient came with an acute emergency with decreased consciousness, shortness of breath, and clammy extremities with a history of frequent vomiting without any fever. The patient was previously diagnosed with CAH and got medicines. Adrenal crisis is acute deterioration in a patient with adrenal insufficiency. The principal clinical manifestation is hypovolemic shock, coma, and marked laboratory which necessitates immediate treatment (Rathbun KM et al., 2021; Bouillon, 2006).

Inadequate cortisol production can lead to hypoglycemia followed by hypotension and fatigue. The symptoms of the illness are more likely to be observed in younger children during periods of sickness or stress. Children with congenital adrenal hyperplasia have low cortisol responses to hypoglycemia (Bowden and enry, 2018). There are 2 types of CAH, the classic and nonclassic. The first type, the classic form, is commonly caused by 21-hydroxylase deficiency. It is a genetic disorder that results in impaired biosynthesis of cortisol with and without aldosterone and epinephrine deficiency. CAH is an autosomal recessive inherited. The clinical manifestation is varied, starting from most severe to mild forms, depending on the degree of severity of the gen defect (Krone and Arlt, 2009). Adrenal crisis can be the first clinical presentation of patients with CAH.

Patients with adrenal insufficiency are often in hypotensive shock and may have paresthesias. They frequently have gastrointestinal symptoms like abdominal pain, nausea, vomiting, diarrhea, and leading to an erroneous diagnosis of an acute abdomen or gastroenteritis. Hypotension is secondary to hypovolemia, but is also due to hypocortisolism, as glucocorticoids exert a permissive effect on catecholamine action (Arlt and Allolio, 2003; Verbalis et al., 2013; Puar et al. 2016). Electrolyte imbalance and hyponatremia are due to aldosterone deficiency. It leads to natriuresis, decreased fluid volume, and hyperkalemia. CAH hypercalcemia can be caused by decreased renal excretion of calcium and increased bone resorption (Arlt and Allolio, 2003).

About 80% of AC was precipitated by concomitant events. The most important trigger factors were respiratory and gastrointestinal infections (Ishii *et al.*, 2018). The majority of patients suffered from AC between 1 and 3 years old, when the respiratory or gastrointestinal infection is usually relatively prevalent (Reisch *et al.*, 2012).

Table 1. Precipitating factor for an adrenal crisis in children with 21-hydroxylase deficiency (21-OHD)

Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%

Source: Ishii T, Adachi M, Takasawa K, et al (2018). Incidence and Characteristics of Adrenal Crisis in Children Younger than 7 Years with 21-Hydroxylase Deficiency: A Nationwide Survey in Japan. Horm Res Paediatr 89, 166-171.

Ventricular fibrillation can be induced by hypoglycemia and hyperkalemia. Hypoglycemia is associated with significant lengthening of the corrected QT interval (QT_C) (Laitinen *et al.*, 2008). It is due to increased catecholamine release during hypoglycemia. The QT_C prolongation could lead to a high risk of ventricular fibrillation and sudden death (Robinson *et al.*, 2003). As potassium increases, the resting membrane potential continues to become less negative, and progressively decreases Vmax. The early effect of mild hyperkalemia on myocyte function is to increase the excitability by shifting the resting membrane potential to a less negative value and thus closer to threshold potential; but as potassium levels continue to rise, myocyte depression occurs and Vmax continues to decrease (Parham *et al.*, 2006).

Hypotension in AC can be explained by a lack of the permissive action of glucocorticoids on adrenergic receptors (Sapolsky, Romero, and Munck, 2000) and by volume depletion caused by a lack of sodium and fluid retention due to missing mineralocorticoid activity. Volume depletion may further be worsened by vomiting and diarrhea (Bancos *et al.*, 2015).

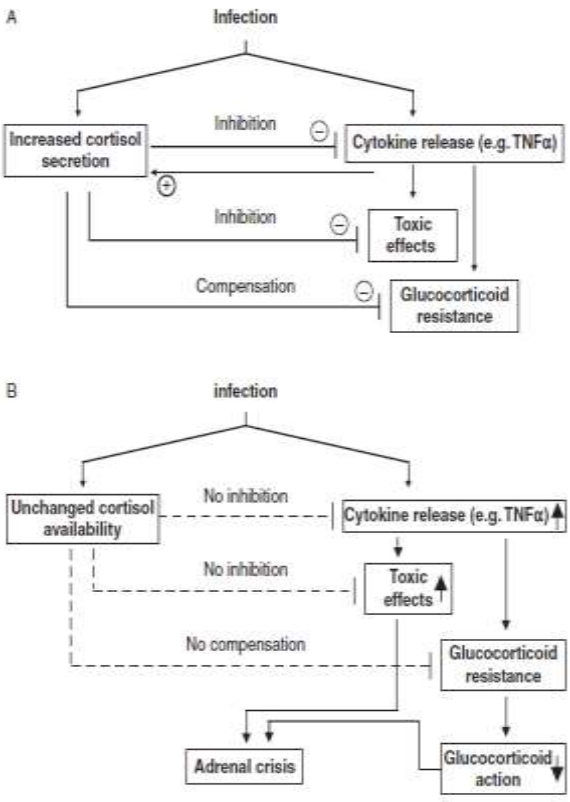
For adrenal crisis with hypotension patients, the resuscitation strategy is similar to treating patients with

sepsis (S Lentz et al.2022). The basic management components of include treating an underlying etiology, stress dose steroids, i.v. fluid resuscitation, glucose, and electrolyte correction. The patient either as a primary presentation of adrenal insufficiency or a known history of adrenal insufficiency with an acute stressor often presents in undifferentiated shock (Charmandari E et al. 2014). Empirical management of adrenal insufficiency should be considered in patients with a limited history and undifferentiated shock. Fever can occur as a symptom of glucocorticoid deficiency or infection. If sepsis is suspected, routine treatment should include cultures followed by empirical antibiotics. Rapid rehydration with 1000 mL of 0.9% saline is recommended (Allolio B. 2015; Charmandari E et al. 2014). The additional fluid administration and fluid composition can then be adjusted based on clinical assessment and electrolyte abnormalities. If hypoglycemia is present giving dextrose-containing fluids are recommended (Charmandari E et al. 2014).

Fever and infection lead to an increase in circulating cortisol levels in healthy subjects. Increment in cortisol levels should be mimicked by adjustment of the hydrocortisone dose in patients with adrenal insufficiency (Husebye *et al.*, 2014). Glucocorticoids influence stress response by permissive, suppressive, stimulatory, and preparative actions (Sapolsky, Romero, and Munck, 2000). While a lack of permissive action of glucocorticoids is highly likely in patients with undiagnosed adrenal insufficiency leading to impaired activation and responsiveness of the cardiovascular system (Sapolsky, Romero, and Munck, 2000).

Infections include interleukin 1 (IL-1), which physiologically stimulates the hypothalamic-pituitary-adrenal (HPA) axis, tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6). Induced the release of cytokines. As a result, cortisol levels increase (Silverman et al., 2005). High levels of glucocorticoids reduce the release and action of cytokines and prevent their potentially harmful effects (Koniaris, Wand, and Wright, 2001). Studies have shown that TNF-α inhibits the function of glucocorticoid receptors and induces a relative state of glucocorticoid resistance (Webster et al.,2001; Van Bogaert et al).,2011). Lack of glucocorticoid inhibitory activity can induce AC through increased TNF-α secretion, increased TNF-α sensitivity, and TNF-α-induced glucocorticoid resistance.

Acute treatment of adrenal crisis is for stabilization, and rehydration, rapid restoration of tissue perfusion. After an IV line is secured, a 20 mL/kg bolus of normal saline (0.9% NaCl) is given over for a period of an hour.



Source: Allolio B (2015). Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol 172(3), R115–R124

Figure 3. Glucocorticoid and cytokine interaction during major infection in patients with intact adrenals (A) and patients with adrenal insufficiency on standard replacement therapy failing to adjust their hydrocortisone doses (B).

If significant hypoglycemia is present, the glucose of bolus 0.2 g/kg (2 mL/kg of 10% dextrose) is given to revive the blood glucose level. Stress doses of glucocorticoid should be administered with a loading dose. Hydrocortisone contains a desirable mineralocorticoid effect in addition to its glucocorticoid effect whereas methylprednisolone and dexamethasone have only a glucocorticoid effect and do not seem to be suitable therapies (Miller WL, Achermann JC, 2008; Ucar, Bas and Saka, 2016; Anang, Utari and Triningsih, 2018).

Ongoing IV steroid therapy consists of hydrocortisone (HC) with a total daily dose of 15-20 in 3 divided doses every 6-8 hours. Hyperkalemia of more than 6 mmol/L can induce fatal cardiac arrhythmias and requires aggressive therapy with intravenous sodium bicarbonate, calcium gluconate, or IV dextrose plus insulin (Miller WL, Achermann JC, 2008; Anang, Utari and Triningsih, 2018).

Table 2. The anti-inflammatory comparison, mineralocorticoid, growth suppressing, and androgen suppressing side effects of commonly used steroids

Steroid	Anti-inflammatory effect	Growth suppressing, glucocorticoid effect, androgen suppressing effect	Salt retention, Mineralo-corticoid activity
Hydrocortisone	1	1	1
Prednisone	4	5-15	0.8
Prednisolone	3.5-4		0.8
Methylprednisolone	5		0.5
Betamethasone	30	0-100	0
Dexamethasone	30	0-100	0
Fludrocortisone	15		200

Source: Uçar A, Baş F, Saka N (2016). Diagnosis and management of pediatric adrenal insufficiency. World J Pediatr 12(3), 261–274.

Education is very important in the management of adrenal insufficiency and the prevention of AC. Patients and families should be informed about CAH, general CAH management, and acute complications which should be taken at home to prevent an adrenal crisis, particularly related to glucocorticoids adjustments in stressful events and AC prevention including administration of emergency glucocorticoid particularly in illness, fever, and any type of stress (Alexandraki and Grossman, 2018). Furthermore, the general practitioners, pediatricians, nurses, and health workers must be aware of these cases. The early detection and prompt treatment can improve the prognosis and quality of life of patients with CAH and AC. Recently, the CAH screening has already been included in the newborn screening suggested in Indonesia.

Prognosis in patients with AC and the mortality of patients with peripheral adrenal insufficiency were increased in some studies. The quality of life of patients with peripheral adrenal insufficiency remains impaired despite the adequate replacement dose but seems to be related to the delay in diagnosis (Alexandraki and Grossman, 2018).

CONCLUSION

The diagnosis of adrenal crisis should be performed as soon as possible to lower the mortality rate and improve the prognosis and quality of life of patients. Moreover, in patients with a shock, patients with a history of disorder of development, especially CAH, the clinician must include an adrenal crisis in the differential diagnosis.

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