OPINION

Diagnosis and treatment of adrenal insufficiency including adrenal crisis: a Japan Endocrine Society clinical practice guideline

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Abstract. This clinical practice guideline of the diagnosis and treatment of adrenal insufficiency (AI) including adrenal crisis was produced on behalf of the Japan Endocrine Society. This evidence-based guideline was developed by a committee including all authors, and was reviewed by a subcommittee of the Japan Endocrine Society. The Japanese version has already been published, and the essential points have been summarized in this English language version. We recommend diagnostic tests, including measurement of basal cortisol and ACTH levels in combination with a rapid ACTH (250 µg corticotropin) test, the CRH test, and for particular situations the insulin tolerance test. Cut-off values in basal and peak cortisol levels after the rapid ACTH or CRH tests are proposed based on the assumption that a peak cortisol level ≥18 µg/dL in the insulin tolerance test indicates normal adrenal function. In adult AI patients, 15–25 mg hydrocortisone (HC) in 2–3 daily doses, depending on adrenal reserve and body weight, is a basic replacement regime for AI. In special situations such as sickness, operations, pregnancy and drug interactions, cautious HC dosing or the correct choice of glucocorticoids is necessary. From long-term treatment, optimal diurnal rhythm and concentration of serum cortisol are important for the prevention of cardiovascular disease and osteoporosis. In maintenance therapy during the growth period of patients with 21-hydroxylase deficiency, proper doses of HC should be used, and long-acting glucocorticoids should not be used. Education and carrying an emergency card are essential for the prevention and rapid treatment of adrenal crisis.

Key words: Adrenal insufficiency, Adrenal crisis, Cortisol, Hydrocortisone, Congenital adrenal hyperplasia

Summary of Recommendations

I. Chronic adrenal insufficiency (AI)
I-1.0 Symptoms

We recommend suspecting AI in patients who have the following symptoms.

I-1.1 Symptoms of cortisol deficiency common to both primary and secondary AI

(1) General fatigue and general weakness; (2) appetite loss and weight loss; (3) gastrointestinal symptoms (nausea, vomiting, constipation and abdominal pain *etc*.); (4) hypotension; (5) mental disorder (apathy, lethargy, anxiety and character change *etc*.); (6) fever; (7) hypoglycemic symptom; and (8) arthralgia.

I-1.2 Symptom of adrenal androgen deficiency common to primary and secondary AI

(1) Loss of axillary and pubic hair in women

I-1.3 Symptoms observed in only primary AI

1) Pigmentation is prominent in gingiva, joints, palm ditch, nail bed, mammary areola, operation scars.

*Of note, pigmentation is sometimes not evident in patients with primary AI, especially in subclinical Addison's disease.

I-2.0 Laboratory examinations

We recommend suspecting AI in patients who show the following general laboratory data and endocrine examinations.

I-2.1 General examinations

(1) Hypoglycemia (fasting blood sugar <70 mg/dL); (2) hyponatremia (serum Na <135 mEq/L); (3) normocytic normochromic anemia (male; <13 g/dL, female; <12 g/dL); (4) low serum total cholesterol level (total cholesterol <150 mg/dL); (5) eosinophilia in peripheral blood (eosinocyte ≥8%); (6) relative leucopenia and lymphocytosis in peripheral blood; and (7) hyperkalemia.

I-2.2 We recommend measuring basal and fasting concentrations of plasma ACTH and serum cortisol in the early morning (before 0900 h).

1) Basal cortisol level in the early morning
(1) ≥18 µg/dL rules out the possibility of AI.
(2) <4 µg/dL is highly suggestive of AI.
(3) ≥4 µg/dL, but <18 µg/dL cannot rule out the possibility of AI.

*As a gold standard for the diagnosis of AI, the insulin tolerance test (ITT), which causes hypoglycemia and then activates the hypothalamic–pituitary–adrenal axis (HPA axis), has been conventionally used. The cut-off value of the peak serum cortisol level in ITT to differentiate AI from normal has been proposed to be 18 µg/dL (500 nM) [1, 2] or 20 µg/dL [3, 4]. In patients with AI, the reference value of basal serum cortisol in the early morning corresponding to the peak value of serum cortisol level <18 µg/dL in ITT has been investigated. Such cut-off values for the diagnosis of AI are summarized in Table 1 [1, 5, 6]. We propose a basal cortisol level <4 µg/dL to be the value that strongly suggests AI, while a basal cortisol level ≥18 µg/dL suggests little possibility of AI.

I-2.3 We recommend confirmatory testing with a rapid ACTH test.

When basal serum cortisol level is in the range <4 µg/dL, or ≥4 µg/dL but <18 µg/dL, a rapid ACTH test (synthetic 1-24 ACTH: CORTROSYN 250 µg iv) is highly recommended. Peak cortisol levels after the rapid ACTH test as shown below indicate the following:

(1) ≥18 µg/dL: usually possible to rule out AI
(2) <18 µg/dL: impossible to rule out primary or secondary AI
(3) <15 µg/dL: a high possibility of primary AI

*When the cortisol value at 30 or 60 min after a rapid ACTH test is ≥18–20 µg/dL, it is usually possible to rule out AI. It has been reported that a peak value <15 µg/dL after a rapid ACTH test is enough to make a diagnosis of primary AI [7]. The cut-off values of cortisol after rapid ACTH tests in various reports are shown in Table 2 [3, 4, 6, 8]. We have adopted a peak cortisol value <18 µg/dL for the diagnosis of AI, including primary or secondary causes, and a peak cortisol value <15 µg/dL for the diagnosis of primary AI.

*When a patient shows a normal response to the 250 µg ACTH test but is positive for anti-adrenal antibody or has other autoimmune diseases, further investigation by the 1 µg ACTH loading test might be recommended to test for subclinical Addison's disease. A low-dose ACTH loading test is now rarely performed. The result

Table 1 Diagnosis of adrenal insufficiency (AI) by basal cortisol level in serum (µg/dL)

Highly suspected	Suspected	Normal	Reference
≤3	3<F<19	19≤	Grinspoon SK *et al*. 1994 [5]
<4 (SAI)	4≤F<17	17<	Erturk E *et al*. 1998 [1]
<5 (SAI)	5≤F≤13	13<	Kazlauskaite R *et al*. 2008 [6]

F indicates cortisol. SAI indicates secondary adrenal insufficiency. As a highly suspected cut-off value of cortisol in AI, we adopted 4 µg/dL. The parenthesis indicates the number of reference.

of the low-dose ACTH loading test might be judged to be normal when the peak cortisol level is ≥20 μg/dL (the accurate value is 19.4 μg/dL). However, when the peak value is <20 μg/dL, there is a possibility of subclinical AI [3]. The peak cortisol cut-off values with a low-dose ACTH test in various reports are summarized in Table 3 [3, 4, 6, 7]. According to a report investigating Japanese patients with latent AI, the peak cortisol value at 30 min after a rapid 1 μg ACTH loading test was <18 μg/dL [9].

I-2.4 We suggest the CRH loading test for the differentiation of the diagnosis of primary or secondary AI.

When the differentiation of primary or secondary AI is needed, the CRH loading test should be considered. In the CRH loading test, peak values of blood cortisol levels as shown below indicate the following:

(1) <18 μg/dL: doubt primary or secondary AI [5].

(2) ≥18 μg/dL: almost rule out pituitary AI and suspect hypothalamic AI [5].

*Plasma ACTH level should be carefully interpreted. Even in the case of secondary AI, basal ACTH level is not always low when a low biological level of ACTH is secreted. In general, when basal ACTH values are within the normal range and the ACTH level at 30 or 60 min after the CRH loading test shows more than a twofold increase over the basal level, pituitary function is usually judged to be normal. When cortisol response to CRH is poor despite a good response of ACTH to CRH, such dissociation may suggest the presence of subclinical Addison's disease [10].

I-2.5 We suggest performing the CRH loading test to observe the response of ACTH (peak value at 60 or 120 min) for differential diagnosis.

(1) A normal or high basal ACTH level and excessive response of ACTH to the CRH test: suspect primary AI; (2) a low or normal basal ACTH level and no or low response of ACTH to the CRH test: suspect pituitary AI; and (3) a low or normal basal ACTH level and a normal response of ACTH to the CRH test: suspect hypothalamic AI or normal pituitary-adrenal function. However, when basal ACTH level is very low (especially below 10 pg/mL), care should be taken to evaluate the responsiveness of ACTH to CRH.

I-2.6 We suggest the ACTH-Z test when primary or secondary AI is not clearly differentiated.

*Even in secondary AI, a low response of cortisol to the rapid ACTH loading test may be observed when patients have been affected for a long time. In such cases, to exclude primary AI, the serial ACTH-Z loading test (CORTROSYN Z 0.5 mg, intramuscular injection for 3 days) may be recommended. However, because this test takes almost 1 week to complete, it is rarely used recently. When urinary free cortisol levels increase by twofold to threefold compared with basal levels, primary AI can be ruled out.

Table 2 Diagnosis of adrenal insufficiency (AI) by peak cortisol level (μg/dL) in serum after rapid ACTH (250 μg) test

Highly suspected	Suspected	Normal	Reference
	(Primary & Secondary AI)	18≤	Dorin RL *et al*. 2003 [8]
		15≤ (Primary AI)	
	(Primary AI)	20≤	Oelkers W *et al*. 1996 [3]
		20≤	Maghnie M *et al*. 2005 [4]
<16 (Secondary AI)	16≤F≤30	30<	Kazlauskaite R *et al*. 2008 [6]

As a cut-off value of cortisol in primary or secondary AI, we adopted 18 μg/dL. As a cut-off value of cortisol in primary AI, we adopted 15 μg/dL. The parenthesis indicates the number of reference.

Table 3 Diagnosis of latent adrenal insufficiency (AI) by peak cortisol level (μg/dL) in serum after low dose ACTH (1 μg) test

Highly suspected	Suspected	Normal	Reference
	(Primary AI & Secondary AI)	20≤	Oelkers W *et al*. 1996 [3]
	(Primary AI)	19.4≤	Laureti S *et al*. 2000 [7]
		20≤	Maghnie M *et al*. 2005 [4]
<16 (Secondary AI)	16≤F≤22	22<	Kazlauskaite R *et al*. 2008 [6]

The parenthesis indicates the number of reference.

I-2.7 We suggest performing ITT when hypothalamic AI is suspected.

The opportunity to perform ITT has also recently decreased because this test causes hypoglycemia, which may induce ischemic heart disease in elderly patients. Thus, the need and indication for the test should be carefully considered. In ITT, when ACTH shows poor or no response and the peak cortisol value is <18 μg/dL, a diagnosis of hypothalamic AI should be considered.

*In AI, insulin sensitivity is enhanced because of cortisol deficiency [11], and an excessive hypoglycemic reaction is often introduced by ITT. Usually, intravenous injection of rapid-acting insulin at a dose of 0.1 U/kg body weight (BW) is recommended. However, when AI is highly suspected, the insulin dose should be scaled down to 0.05 U/kg.

## I-2.8 We suggest an algorithm for the diagnosis of primary or secondary AI (Fig. 1).

I-3.0 Treatments of AI

I-3.1 We suggest the following twice-daily hydrocortisone (HC) (Cortril®) doses.

10 mg/day	morning 7.5 mg	evening 2.5 mg
15 mg/day	morning 10 mg	evening 5 mg
20 mg/day	morning 15 mg	evening 5 mg

I-3.2 We suggest the following thrice-daily HC (Cortril®) doses [12].

First, the morning dose of HC should be calculated as 0.12 mg × BW (kg), after which the dose of the daily profile should be calculated using the ratio 3:2:1. For example, when BW is 55–74 kg, 7.5 mg in the morn-
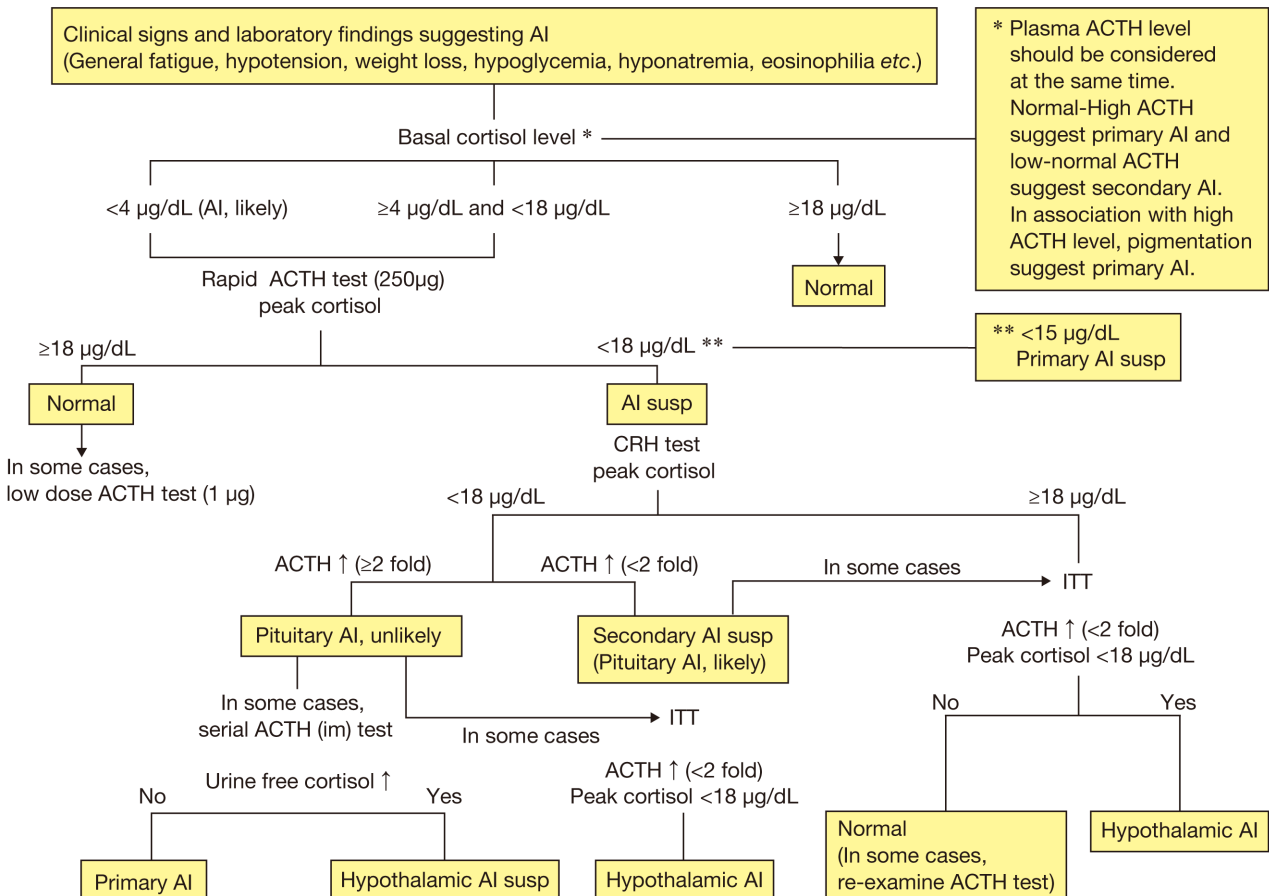
Fig.1 A diagnostic algorithm of AI

AI indicates adrenal insufficiency. No need to follow every examination and perform as needed. Usually, basal levels of plasma ACTH and serum cortisol are very informative and suggest examinations for the differential diagnosis of primary or secondary AI.

ing, 5.0 mg in the afternoon and 2.5 mg in the evening (total 15 mg) is recommended. By this method, blood cortisol level has been shown to mimic the physiological diurnal rhythm of cortisol.

*From the perspective of disease prognosis, it is currently recommended to achieve optimal replacement therapy, which mimics the physiological level and rhythm of cortisol secretion as much as possible. Reports suggests that physiological production of cortisol is 5–7 mg/m^2 per day [13] or 9–11 mg/m^2 per day [14]. These data provide the basis for 10–20 mg/day HC replacement doses in patients with AI. Given that Japanese individuals tend to ingest a relatively large amount of salt, replacement with HC (Cortril®) 10–20 mg/day only is usually sufficient. The medication is usually given 2–3 times per day. In the case of twice-daily dosage, the morning and evening ratio is recommended to be 2:1. According to one report [15], some quality of life (QOL) scores in patients with thrice-daily HC medication were worse than those in patients with twice-daily HC medication.

I-3.3 We highly recommend 2–3 times the usual HC dose in patients with AI for the prevention of adrenal crisis in during sickness or strong physiological stress.

I-3.4 We suggest that when salt-losing symptoms such as hyponatremia and low blood pressure are observed despite replacement with Cortril®, Florinef® at a dose of 0.05–0.2 mg once in the morning be added.

*In secondary AI, because the renin-angiotensin (R-A) system is maintained, Florinef® is usually unnecessary. However, in primary AI, the drug is sometimes necessary when salt-losing signs are observed despite the replacement of glucocorticoid (GC). For proper dose setting of Florinef®, the presence or absence of edema, blood Na and K concentration, urinary Na excretion, PRA *etc*. should be monitored. Full normalization of plasma renin activity (PRA) may result in hypertension, edema and low K concentrations; therefore, it is better to set PRA in the high normal range [16].

I-3.5 We recommend changing the dose of Cortril® when the drug effect is not fully observed because of interference between Cortril® and other drugs used concomitantly.

*The drugs for which it is necessary to increase HC dose because of the induction of drug-metabolizing enzymes (such as CYP3A4) are rifampicin [17, 18], anti-epileptic agents such as phenytoin, phenobarbital, carbamazepine, valproic acid, primidone and ethosuximide, and antihypoglycemic agents, such as pioglitazone.

*It is sometimes necessary to increase the GC replacement dose when mitotane is prescribed because of its enhancing effect on cortisol binding globulin (CBG) [19, 20].

*Estrogens are also drugs that can increase CBG, leading to an increase in serum cortisol levels, but there is usually no need to increase the GC replacement dose.

*When growth hormone (GH) replacement is started in patients with AI because of combined GH deficiency, a decrease in the serum cortisol level may occur due to the GH-induced inhibitory effect of 11β-hydroxy steroid dehydrogenase type 1 (11β-HSD1) activity, which is responsible for the conversion of cortisone to cortisol. Therefore, after GH supplementation, if AI symptoms are observed, increasing the dose of Cortril® should be considered [21, 22].

*When the following agents, which may enhance the effect of HC, are concomitantly given with GC, a reduction of the GC dose may be needed [23-26]. Such drugs that inhibit the activity of CYP3A4 include diltiazem, cimetidine, aprepitant, itraconazole, ritonavir (and other anti-retroviral drugs) and fluoxetine (and other selective serotonin reuptake inhibitors), *etc*.

I-3.6 When AI is complicated with hypothyroidism, we recommend using HC first before thyroid hormone.

*In the case of AI due to Schmidt syndrome or secondary AI due to hypothalamic-pituitary lesions, AI can be complicated with primary or secondary hypothyroidism. In such cases, replacement of HC should occur before thyroid hormone treatment. This order is important because thyroid hormone enhances the turnover of HC, which may cause an exacerbation of AI or, at worst, adrenal crisis [27].

I-3.7 We suggest taking note of the occurrence of central diabetes insipidus (DI) when starting GC replacement in secondary AI.

*Central DI is a risk factor for the development of acute AI [28]. In the case that AI is complicated with central DI, DI is masked [29] and becomes overt after GC replacement.

I-4.0 Replacement therapy under special circumstances

I-4.1 In the perioperative period, for the prevention of adrenal crisis, we suggest the following dose of HC according to the degree of the invasiveness of surgery: HC 30–50 mg/day for minor surgery, 25–75 mg/day for mild to moderate surgery and 150 mg/day for major surgery.

*The above doses may be administered for a few days, and thereafter it is possible to decrease the doses gradually. In the case of adrenal crisis, administration of 200–300 mg/day of HC with infusion of saline (initially 0.5–1.0 L/h) containing glucose should be considered [30] (see details in the section on acute AI below).

I-4.2 Pregnancy and labor

(1) The dosage of HC we suggest for pregnant women with AI is 12–15 mg/m^2 [31].

*Owing to the increase in levels of free cortisol in late pregnancy, the necessity of increasing the HC dose during this period is controversial.

(2) When administering a synthetic GC during pregnancy, we recommend the use of prednisolone because its placental transportability is very low.

(3) We strongly recommend that fluorinated steroids should not be used during pregnancy. Such steroids show high placental transportability, raising a possibility of intrauterine growth retardation.

(4) Administration of pharmacological doses of GC in early pregnancy should be limited to cases of maternal necessity and emergencies. It is necessary to explain to the patient that there is an increased risk that the baby will develop cleft lip and palate.

(5) High doses of HC (50 mg every 6 h) are recommended from the onset of labor to 48 h after birth. At the time of delivery, an intravenous bolus injection of 50 mg HC should be started, and then increasing doses of HC should be considered, depending on the progress of the delivery.

(6) In the case of Caesarean section, intravenous injection of 100 mg HC followed by successive intravenous injections of a decreased HC dose, 50 mg or 25 mg every 6–8 h until 48 h, might be considered. After 48 h, restarting the usual oral dose of HC could be considered.

*Given that progesterone levels increase with advanced gestational age and antagonize aldosterone binding to mineralocorticoid (MC) receptor, an increase in the dose of MC is sometimes necessary in late gestation [16].

I-4.3 When GC medication is stopped in patients who have been medicated for a long time, we recommend that the GC dose be tapered, and that attention be paid to the possibility of acute AI.

*When supraphysiological amounts of GC are administered for a long period of time, the endogenous HPA axis is suppressed [30, 32, 33]. In such patients, when medication is stopped or rapidly tapered, adrenal crisis may take place. Not only oral but also nasal [34], transdermal [35] or transbronchial [36] administration of GC can suppress the HPA axis. According to a report from the United Kingdom [36], 23 of 2,900 patients had a low blood sugar level after use of inhaled GC. Most of these patients had inhaled more than 500 µg/day fluticasone.

I-4.4 Cushing's syndrome after surgery

(1) In Cushing's syndrome (primarily due to adrenal adenoma) or Cushing's disease (caused by pituitary ACTH-producing adenomas), GC replacement is immediately needed after adrenalectomy or Hardy's operation, respectively, and the replacement therapy should be continued by GC tapering until recovery of adrenal insufficiency (usually 12–18 months).

(2) We recommend that 100–200 mg of intravenous hydrocortisone sodium succinate is given at the time of tumor extirpation. This initial dose should then be given over 24 h by intravenous infusion. From the next day, while observing symptoms, the HC dose should be gradually tapered to 100 mg, 75 mg and 50 mg per day. A hyperthyroid state due to the syndrome of inappropriate TSH secretion [37] is sometimes observed owing to the rapid tapering of HC, in which case we suggest gradual decreases in the dose of HC.

I-5.0 Educational points for patients with AI

(1) Do not stop the oral intake of GC by your own judgment.

(2) During physical stress, for example, flu, fever, tooth extraction or strong exercise (such as a long walk), take 1.5–3.0 times the usual dose of Cortril®.

(3) Recognize that missed doses or insufficient steroid doses at a time of stress could cause adrenal crisis, which is characterized by remarkable general malaise, nausea, vomiting, fever, abdominal pain and symptoms such as low blood pressure. When the condition becomes more severe, consciousness disorder and

hypovolemic shock can occur.

(4) Carry an emergency card including the disease name, treatment, a contact person and details of the doctor in charge of your care at all times.

Supplementary comments and evidence
[Pathophysiology]

Primary AI is characterized by the impaired production of adrenal steroids, including aldosterone, cortisol and adrenal androgens. Idiopathic adrenal atrophy by autoimmune mechanisms or tuberculosis account for the majority of cases of adult AI, and such acquired cases of primary AI are called Addison's disease. Congenital types of primary AI include congenital adrenal hyperplasia, congenital adrenal hypoplasia and familial glucocorticoid deficiency (FGD). Diagnostic criteria of congenital adrenal diseases have been proposed by the research committee of adrenal disease of the Ministry of Health, Labour and Welfare of Japan in collaboration with the Japan Endocrine Society [38].

Congenital cases are affected by AI in the long-term, beginning from the early onset in infancy or childhood. Sudden events such as trauma, hemorrhage and infarction, *etc*. cause acute AI. Secondary AI caused by lesions of the HPA axis results in impaired ACTH synthesis, leading to impaired production of cortisol and adrenal androgens from the adrenal gland. In the case of secondary AI, aldosterone production is usually preserved because the R-A system is preserved. Causes of secondary AI include pituitary tumors, lymphocytic hypophysitis, craniopharyngioma, germinoma and treatments including surgery and radiation [3].

Pigmentation is a clinical sign specific to primary AI. Along with cortisol deficiency, the secretion of the proopiomelanocortin (POMC)-derived peptides ACTH and γ-MSH, which induces pigmentation, is increased from the anterior pituitary gland.

Primary AI is caused by various etiologies from congenital disease to acquired disease. In a narrow sense, acquired etiologies such as autoimmune mechanisms (idiopathic) or infections, including tuberculosis, fungal and viral infections, as a cause of AI are referred to as Addison's disease. In the autoimmune type of Addison's disease, anti-adrenal antibodies (the antigens are usually adrenal steroidogenic enzymes such as P450c21 and P450c17) are often detected. Congenital causes of primary AI include genetic abnormalities in genes such as *DAX-1* and *SF-1* are a cause of congenital adrenal hypoplasia. The incomplete form of *StAR*

abnormality does not involve genital abnormality, thus it has sometimes been categorized as Addison's disease in childhood. Congenital adrenal hypoplasia complicated with intrauterine growth restriction, metaphyseal dysplasia and genital anomalies is known as IMAGe syndrome, and its genetic cause is a gain of function mutation of the cyclin-dependent kinase inhibitor 1 (*CDKN1C*) gene.

FGD shows an autosomal recessive mode of inheritance, and it is a condition that is refractory to ACTH stimulation and causes AI. The genetic causes of ACTH insensitivity include abnormalities of MC2R (melanocortin 2 receptor) and MRAP (melanocortin 2 receptor accessory protein). Gene mutations that have recently been shown to cause FGD include abnormalities of the gene that encodes the mitochondrial enzyme NNT (nicotinamide nucleotide transhydrogenase) and the gene that encodes thioredoxin reductase 2 (TXNRD2). Given that NTT and TXNRD2 act as an anti-oxidation system in mitochondria, the importance of mitochondrial redox control in steroidogenesis has been clarified [39, 40].

Other diseases that cause ACTH insensitivity include AAA (triple A) syndrome. Triple A syndrome is an autosomal recessive disease complicated with the triad of esophageal achalasia, alacrima and AI, and also with muscle atrophy and muscle weakness. Mutation of the *ALADIN* gene is a genetic cause of triple A syndrome. Idiopathic Addison's disease includes the category of autoimmune polyglandular endocrine syndrome (PGA) or also called autoimmune polyendocrine syndroeme (APS). Type I is complicated with at least two of the triad, Addison's disease, idiopathic hypoparathyroidism and skin candidiasis (HAM syndrome: hypoparathyroidism–Addison–moniliasis). In type 2 PGA, Addison's disease is complicated with either or both of autoimmune thyroid disease (Hashimoto's disease or Graves' disease) and type 1 diabetes. The genetic etiology of type 1 PGA has been reported to involve the *AIRE* gene, but that of type 2 is unknown.

Most cases of secondary AI are caused by organic lesions of the hypothalamic–pituitary region. Lymphocytic hypophysitis caused by autoimmune pathologies exhibits a reversible time-course in endocrinology and on the MRI image by natural course or steroid administration in recent years; lymphocytic hypophysitis may also develop as a result of IgG4-related syndrome in some cases [41].

[Epidemiology]

According to an annual report of a nationwide survey of adrenal diseases in 2011 in Japan investigating the period 2003–2007, the domestic incidence of primary AI has been estimated at 911 persons in 5 years [42]. Autoimmune type, infectious type and others were 49%, 27% and 11%, respectively. The infectious causes consisted of tuberculosis (57%), fungal infection (3%) and others (5%). Compared with the similar nationwide investigation in 1998, idiopathic cases have increased along with a decrease in tuberculosis in Japan. In the total number of 127 cases (70 males and 51 females), the average age was 64.8 years (men 63.2 years, women 65.6 years) [42]. In a German report investigating the etiology of 254 cases of primary AI, 165 cases (65%) were found to be idiopathic while tuberculosis was the cause of only six cases (2.3%) [28]. According to a nationwide epidemiological study of secondary AI in Japan in 2000, the number of adult hypopituitarism cases including both men and women has been estimated to be about 7,000. Neoplastic lesions including pituitary tumors, craniopharyngiomas, germ cell tumor, *etc*. were the cause in more than 50% of cases. A similar result has been reported in Germany, indicating that the pathogenesis of secondary AI in 290 cases included 107 cases of pituitary adenomas (36.8%), 30 cases of other intracranial tumors (10.3%) and 12 cases of Sheehan's syndrome (4.1%) [28].

[Symptoms]

Pigmentation is observed in almost 90% of typical cases of primary AI [42]. Other commonly observed signs of primary and secondary AI include general fatigue, gastrointestinal symptoms, low blood pressure and joint pain. In most female patients with AI, loss of axillary or pubic hair is observed as a sigh of DHEA deficiency, because such hair growth depends on DHEA. The diagnostic value of axillary or pubic hair loss for AI in female patients is high. However, in the case of subclinical AI, gastrointestinal symptoms may be present with a certain degree of general fatigue, and pigmentation is usually not evident [9].

[General laboratory examinations]

In AI due to tuberculosis, not only adrenal cortical function but also adrenal medulla function is sometimes affected. In such cases, the response of urinary catecholamines to ITT is disturbed. By contrast, adre-nal medulla function is left relatively intact in idiopathic AI. This difference is sometimes useful for the differentiation between idiopathic AI and Addison's disease caused by tuberculosis. Idiopathic Addison's disease is often complicated with other autoimmune diseases, and sometimes comprises PGA. In PGA, functional testing of multiple endocrine organs and examinations of antibodies in each organ are necessary. It should be noted that anti-adrenal cortex antibodies are found in about 40% to 70% of idiopathic Addison's disease cases, but also found in about 10% of cases of the tuberculosis type of Addison's disease. The differentiation of etiology between tuberculosis or idiopathic is comprehensively judged by the presence or absence of old or active tuberculosis, adrenal medulla function, and the presence or absence of an autoimmune disease background. The presence of calcification in the lung or adrenal portion on X-ray is an important finding, suggesting the possibility of tuberculosis as a cause of Addison's disease. In the early stage of the onset of tuberculotic Addison's disease, adrenal glands examined by abdominal CT reveal swelling rather than atrophic adrenals. In idiopathic Addison's disease, atrophic adrenals are observed. In secondary AI, the presence or absence of inflammation and space-occupying lesions in the pituitary and suprasellar hypothalamic regions should be examined by MRI.

Not only anti-adrenal antibodies, but also antibodies against other organs, such as the ovary, testis, placenta and pancreas, as well as anti-intrinsic factor antibodies and anti-thyroid antibodies are present in idiopathic AI in patients with PGA. In secondary AI, if hypophysitis is suspected based on pituitary MRI findings, the measurement of anti-pituitary antibodies and/or IgG4 is recommended.

[Endocrinological examinations]

(1) Basal ACTH level

Currently, blood ACTH is measured by a non-RIA measurement system using a chemiluminescence and fluorescence method. Blood ACTH level depends on the antibody against ACTH in the measurement kit. For example, a monoclonal antibody against c-terminal ACTH, ECL antibody (Roche), specifically recognizes proACTH but does not recognize POMC. This antibody does not recognize part of big ACTH. However, polyclonal antibodies against c-terminal ACTH in the TOSOH II kit (Tosoh Corporation) recognize any type of big ACTH. Thus, even in the case of ACTH defi-

ciency, plasma ACTH level is not always low when biologically inactive ACTH is secreted. Also, the measurement of plasma ACTH in the low concentration region is currently considered to be less reliable. The proposal of an absolute diagnostic value of plasma ACTH for the diagnosis of AI is not realistic.

(2) Urinary free cortisol

The majority of blood cortisol binds to CBG and 8–10% is free cortisol. Free cortisol is filtered by glomerular, most of which is reabsorbed in the renal tubules, and 1–5% of the filtered cortisol is excreted in the urine. While cortisol measurement in urine is very useful in the diagnosis of Cushing's syndrome, it is not recommended as a diagnostic test of AI because of the inaccuracy of 24h urine collection and the varied values between individuals in low range of urinary free cortisol. The free fraction of cortisol increases with transient saturation of CBG immediately after the oral intake of HC, thus leading to an increase of free cortisol in the urine [43]. Thus, the effectiveness of urinary cortisol as an indicator of correct HC supplementation has been also questioned.

[Treatments in general]

In Japan, replacement with Cortril® 10–20 mg/day in AI patients is common based on the fact that cortisol secretion rate is 5–10 mg/m^2/day. In general, adrenal function is relatively preserved in secondary AI due to hypothalamic–pituitary lesions and requires a reduced HC dosage compared with primary AI, namely 10–15 mg/day. According to the responses to a questionnaire for doctors in the Japan Steroid Hormone Society in 2006 (38 doctors responded, including 29 internal medicine doctors), in primary AI, prescription of 20 mg Cortril® (morning 15 mg, evening 5 mg) was 3.5 times more frequent than 15 mg Cortril® (morning 10 mg, evening 5 mg). By contrast, in the case of secondary AI, the frequency of both of these prescriptions was roughly equal, supporting the tendency of smaller doses of HC in secondary AI than primary AI.

In order to mimic the diurnal rhythm of cortisol, a larger dose of HC is administered in the morning than the evening. Although oral HC administration after breakfast is common, administration before breakfast may be preferable in order to achieve an earlier increase in serum cortisol at the start of the day [12]. Also, administration of HC adjusted by BW (0.12 mg/kg) makes it possible to minimize individual differences in blood cortisol fluctuation [12].

[QOL]

Recent clinical epidemiological studies of GC replacement in adult patients with AI suggest that excess doses of GC reduce patients' QOL, and in the long term, induce metabolic abnormalities, leading to an increase in cardiovascular disease. Thus, an optimal dose of GC for adequate replacement is generally recommended. In 334 AI patients (194 primary AI and 140 secondary AI), QOL (SF-36, GBB-24, Hospital Anxiety, HADS) was evaluated in patients with different HC doses. The group who received >30 mg/day HC showed a poor SF-36 score in terms of physical function and total well-being and a poor CGB-24 global score and scores related to heart symptoms and stomach symptoms [44]. In the above study, compared with patients with primary AI, those with secondary AI showed a greater decrease in well-being [44].

Another study including 235 primary AI patients and 195 secondary AI patients divided the patients into five groups by HC replacement dose and QOL was investigated by questionnaire [15]. No statistical difference was found between the five groups with primary AI. However, in secondary AI, overall health, well being and vitality were significantly decreased in the group receiving more than 30 mg/day HC [15]. As to the frequency of HC medication, despite the same total HC replacement dose per day, thrice a day medication negatively affected QOL more than twice a day medication, especially in social-life function and physical function [15].

[Perioperative GC replacement]

For perioperative steroid supplementation in patients with chronic AI, fine dosing is proposed according to the degree of invasiveness of the surgery [16]. According to Hahner et al. [45], the following protocols are recommended. For minor surgery under local anesthesia, increase the GC dose to 2–3 times the conventional dose or increase the dose to 25–50 mg/day, and when surgical stress is moderate, increase the GC dose to 50–75 mg/day. For major surgery under general anesthesia, use an intravenous drip infusion with 150 mg HC diluted in a 5% glucose solution for 24 h from the start of surgery, then an intravenous injection of HC the next day, and then a rapid decrease in the HC dose back to the conventional oral dose of HC. These protocols are based on the following findings. Serum cortisol level in individuals with normal adrenal function reaches a peak at the time of tracheal extuba-

tion immediately after the end of surgery [46, 47] and returns to the normal range within 48 h [48]. The blood cortisol concentration rises above the physiological range by intermittent bolus injection of HC [49, 50]. Furthermore, according to Salem *et al.* [51], in seven studies investigating cortisol secretion after major surgery, the average cortisol secretion was less than 200 mg/day except for one study.

Glowniak *et al.* [48] performed a small, double-blind study of steroid supplementation in subjects with secondary AI who underwent surgery. The researchers concluded that no increase in the HC dose in the perioperative period in secondary AI was necessary because no acute AI occurred in the group who did not receive an increased HC dose. Nevertheless, we feel that this result cannot be generalized from a medical safety standpoint. Given that there is no special basis for the validity of an HC dose of more than 200 mg/day in the perioperative period, the HC dose should be decreased as soon as possible if postoperative complications are not detected.

[Pregnancy]

In healthy pregnant women, as gestational age advances, blood ACTH and cortisol values increase. Basal cortisol values in the early morning in pregnancy are reported to be 9.3 ± 2.2 μg/dL in the first trimester, 14.5 ± 4.3 μg/dL in the second trimester and 16.6 ± 4.2 μg/dL in the third trimester [52]. The peak value of cortisol in response to an ACTH loading test also increases more in late pregnancy than in the non-pregnant state [52]. An increase of cortisol in late pregnancy is thought to be caused by the antagonistic effect of progesterone on GC action and also by the increase in CBG [53].

A replacement dose based on clinician experience ($12–15$ mg/m^2) has generally been used in pregnancy [54]. By contrast, to overcome the increase in free cortisol in late pregnancy [53], an increase of $5–10$ mg HC in this period is recommended [55]. However, no evidence has been proposed to support the necessity of this recommendation.

Since prednisolone is also largely inactivated by 11βHSD2, the rate of placental transfer of prednisolone to the fetus is low, with the value of about 10%. However, as synthetic fluorinated steroids are not inactivated by 11βHSD2, placental permeability is high and there is a possibility that the fetus is exposed to synthetic GC from the mother. Permeability is reported to be 100% for dexamethasone and 30–50% for betamethasone [56]. Thus, the use of HC or prednisolone [48, 57] is highly recommended during pregnancy. However, in one study, no abnormalities of the central nervous system including mental retardation were found in newborn children who were exposed to pharmacological doses of maternal dexamethasone during pregnancy [58]. When pregnant women are exposed to high concentrations of GC, especially in early pregnancy, because of reasons such as surgery, the frequency of entire malformation is not significantly increased, but the frequency of oral clefts is increased to 3-4 people per 500–700 people, compared with the natural incidence of one in 700 people. A threefold to fourfold increase in the risk of oral clefts has been reported [59, 60]. However, epidemiological studies of the effects of different doses and types of steroids have not been performed.

[Cushing's syndrome]

Cushing's syndrome is characterized by chronic cortisol excess and the etiology includes Cushing's disease, cortisol-producing adrenal tumors, ectopic ACTH-producing tumors and bilateral macronodular adrenal hyperplasia. In the postoperative period, no matter what the etiology is, GC replacement therapy is essential because of the suppression of the normal HPA axis after surgery. Even in subclinical Cushing's syndrome, atrophy of the healthy side of the adrenal gland is observed to some extent, and it is necessary to start GC replacement after surgery in a similar manner to that in Cushing's syndrome [61]. In the case of Cushing's syndrome due to an adrenal adenoma, GC replacement started with 15–20 mg Cortril® can be gradually tapered along with the degree of AI symptoms and ACTH values. The replacement period has been reported to be 1 year and 8 months (3 months to 7 years and 3 months) [62]. The longer the duration of Cushing's syndrome, the longer the replacement of HC after adrenalectomy is [63]. In the process of tapering HC, steroid withdrawal syndrome can be observed even with 20 mg HC [64], and the syndrome of inappropriate TSH secretion may take place, which may lead to symptoms of steroid withdrawal syndrome [37]. In such cases, gradual tapering of HC is necessary. When final recovery of the HPA axis is confirmed by measuring ACTH and cortisol levels, it is possible to stop HC medication.

[Sickness and adrenal crisis]

About 40% of chronic AI patients have been reported to experience an adrenal crisis [28]. Cortisol secretion in healthy individuals is around 5–10 mg/m^2 (20–30 mg/day) [13]. However, at times of stress, cortisol production is known to increase up to 300 mg/day [65]. In AI patients, 2–3 times the usual amount of p.o. HC or 30–50 mg/day in mild stress (fever and chills, *etc*.), might be sufficient until recovery. In the case of strong physical stress (surgery, trauma requiring general anesthesia, delivery and intensive care, *etc*.), continuous infusion of 150 mg HC in a 5% glucose solution for 24 h and 100 mg HC the next day might be advised.

If diarrhea and vomiting are present, intravenous HC administration is desirable. When performing exercise, oral administration of 5–10 mg HC 1–2 h prior to exercise is desirable [30]. Relatively detailed examples of HC doses for various kinds of stress are shown [66].

In order to avoid a crisis, patients and their families should be educated about the need to increase the replacement dose of HC during sickness or physical stress. When an adrenal crisis develops and proper treatment is not started, hypovolemic shock with unconsciousness can take place. It is very important to prepare an emergency card and advice patients to carry it constantly.

[Modified-release hydrocortisone]

It is impossible to exactly reproduce the circadian rhythm of endogenous cortisol by current HC treatment. In this sense, a drug to mimic the circadian rhythm of cortisol has long been desired and has been developed by modifying the release of HC, and named modified-release HC (MRHC). A drug from Phoqus Pharmaceutical taken p.o. at 2200 h closely reproduces the physiological circadian rhythm of cortisol. With this drug, a bottom value of cortisol, 2.0 μg/dL at 0018 h, and a peak value of cortisol, 15.5 μg/dL at 0832 h, has been shown using healthy men whose endogenous cortisol secretion was inhibited by dexamethasone [67].

The pharmacokinetic evaluation of another MRHC, 20–30 mg Chronocort® p.o., similarly mimicked the endogenous cortisol secretion pattern under the condition that endogenous cortisol secretion was suppressed by dexamethasone in healthy male subjects. By taking 30 mg Chronocort® divided into doses at two tooth brushing times, namely before sleep and after getting-up, the blood cortisol level in the afternoon remained constant, with an average value over 200 nmol/L (7 μg/dL). The use of this drug in patients with 21-OHD is useful for the improvement of the disease because of the suppression of an early morning surge in ACTH [68]. In addition, MRHC that combines a drug coating that allows the early release of HC within 20 minutes as well as the sustained release of cortisol has been developed, and its pharmacokinetic profile is also close to physiological replacement when it is administered to patients with AI [69].

[Prognosis]

Bergthorsdottir *et al*. [70] investigated the life expectancy of patients with primary AI in Sweden (1,675 people) by retrospectively following-up patients for an average of 6.5 years after the diagnosis, and comparing life expectancy to that of the control population. Death of 507 primary AI patients occurred during the study period, which far exceeded the predicted value of 199 people. Overall mortality risk was 2.19 in men (95% confidence interval 1.91–2.51) and 2.86 in women (95% confidence interval 2.54–3.20) [69]. As to the cause of death, rates of cardiovascular disorders, malignant disease and many infectious diseases were relatively high. Death due to endocrine abnormalities was observed in 64 patients, and deaths due to AI itself were observed in 36 patients (15%, the second highest cause of death) [70]. Thus, in patients with diagnosed AI, adrenal crisis still occurred, and in some cases resulted in death. Other studies report that mortality risk in primary AI is not increased overall, but that premature death is increased in young people [71].

II. Acute AI (adrenal crisis) in adults
II-1.0 Symptoms

(1) Various symptoms are observed, such as nausea, vomiting, abdominal pain, muscle pain, arthralgia, fatigue, high fever, low blood pressure or disturbance of consciousness. If the patient has more than a couple of these symptoms, he may be in adrenal crisis. Patients are sometimes misdiagnosed as having acute abdomen.

(2) As to physical examinations, signs suggesting the presence of chronic AI give high diagnostic values.

(3) The possibility of AI is suggested in patients who have received long-term continuous steroid treatment. Such patients may show Cushing phenomenon in their appearance.

II-2.0 Laboratory examinations

(1) Findings are almost the same but augmented compared with those observed in chronic AI.

(2) Patients in adrenal crisis are under strong physiological stress, and immediate diagnosis by occasional blood sampling should be the first priority.

(3) The following serum cortisol levels at occasional blood, <3–5 μg/dL suggest high possibility of adrenal crisis [72].

II-3.0 Treatments of adrenal crisis

II-3.1 We recommend that if there is a possibility of adrenal crisis, treatment should be started immediately just after taking the blood sample.

II-3.2 We strongly recommend intravenous administration of HC [16].

Table 4 shows typical treatments of adrenal crisis [66]. Usually, HC is administered with saline and glucose solution.

II-3.3 During sickness, the dose of steroid administration should be increased, depending on the level of severity of the sickness.

Supplementary comments and evidence
[Pathophysiology]

Adrenal crisis is an acute onset of AI, which could lead to a fatal condition if not treated. There are many triggers such as various stress attack (infection, injury, *etc*.) in patients with known or unknown chronic AI, and excessive reductions or inadequate discontinuation of steroid treatment. One of the most common triggers of adrenal crisis is infection, especially gastrointestinal infections [28]. The occurance of adrenal crisis is reported to be associated with female sex, DI, asthma and diabetes mellitus [28].

The major pathophysiology of adrenal crisis is acute

Table 4 Treatment in adrenal crisis

1) Intravenous drip infusion of 500-1,000 mL/h saline under the monitor of cardiac function.
2) After intravenous injection of 100 mg hydrocortisone (HC), intravenous drip infusion of 5% glucose containing 100-200 mg (HC) for 24 hours. Or intravenous injection of 25-50 mg HC every 6 hour.

The amount of saline infusion should be changed according to age and complicated diseases. Cited from reference 66 and modified.

circulatory failure. Dysregulation of various hormonal and humoral factors also contribute to the pathophysiology. For example, body fluid loss, including sodium, induced by depletion of GC and MC, and disturbed production of catecholamines and circulatory failure brought about by the primary disease itself may also contribute to the pathogenesis of adrenal crisis.

[Epidemiology]

According to a report, 44% of patients with AI receiving GC replacement had experienced adrenal crisis more than once, and the estimated ratio was 6.3 events/100 patients/year [28]. In addition, adrenal crisis requiring medical treatment was seen in 8% of patients with Addison's disease [73]. Etiological research in Japan reported that the leading cause of adrenal crisis was infection, which accounts for more than 50% of cases, and the second most common cause was discontinuation of steroid treatment [42].

[Prognosis]

A retrospective study with 1,675 patients with primary AI followed-up for an average of 6.5 years reported that 36 patients (15%) died from adrenal crisis, which was the second most common cause of death [70]. Death by adrenal crisis can happen even in patients previously diagnosed with AI. Education about self-injection of GC has been suggested to be important for the prevention of adrenal crisis, independent of general education about AI to patients [28].

III. Chronic or acute AI in childhood
III-1.0 Pathophysiology

(1) Etiological disorders of acute AI of childhood are almost the same as those of adulthood, but the incidence of congenital disorders is much higher in children.

(2) Congenital adrenal hyperplasia and congenital adrenal hypoplasia are common causes of congenital AI.

(3) Acute AI of childhood occurs from dysfunction of the HPA axis or sudden cessation (steroid withdrawal syndrome) or inadequate supplementation of GC in chronic AI. Severe infectious disease, operation and physical stress are common risk factors of acute AI, but sometimes it occurs without any cause.

III-2.0 Laboratory examinations

Very similar findings are observed in adulthood and childhood. Please note that steroid profiles and complicated diseases have different findings according to

the subtypes of congenital disorders, including congenital adrenal hyperplasia, congenital adrenal hypoplasia and ACTH insensitivity syndrome [38]

III-3.0 Treatment of chronic AI in children

III-3.1 Treatment of chronic AI caused by adrenal hypoplasia *etc*. (Table 5)

(1) Administer HC in primary AI: 10–20 mg/m^2/day in newborn babies and infncy, 10–15 mg/m^2/day in childhood and school-age children.

(2) Administer HC <10 mg/day in secondary AI.

(3) Despite HC administration, the dose of fludrocortisone in cases of salt losing is 0.025–0.2 mg/day, regardless of age.

(4) Management in sickness (see section on acute AI)

*The cautions concerning masked DI in secondary AI patients and hormone replacement orders in AI cases complicated with hypothyroidism are the same as those stated for adult AI.

III-3.2 Treatment of congenital adrenal hyperplasia due to classic type of 21-hydroxylase deficiency (21-OHD) [74-76].

(1) In the initial treatment of neonatal classical type 21-OHD, in order to suppress adrenal androgen production, we recommend relatively higher doses of GC administration than those for maintenance therapy (Table 6).

(2) In maintenance therapy during the growing period of classical type 21-OHD, we recommend HC administration.

(3) The long-acting formulation of GC should not be used because of its impact on growth retardation.

(4) In neonates and infants with the salt-losing type, we recommend fludrocortisone and sodium chloride.

Table 5 Glucocorticoid dose of AI in children

	Administration	Drug	Dose	
Acute AI	Intravenous (Intramuscular *)	Hydrocortisone sodium succinate (Solu Cortef R, Saxizon R) Hydrocortisone sodium phosphate (Hydrocortisone R)	Neonate **	10-20 mg/kg/day
			Infancy **	2-10 mg/kg/day
			Childhood **	2-10 mg/kg/day
			School–aged **	2-10 mg/kg/day
Chronic AI	Oral	Hydrocortsione (Cortril R)	Neonate	10-20 mg/m^2/day
			Infancy	10-20 mg/m^2/day
			Childhood	10-15 mg/m^2/day
			School–aged	10-15 mg/m^2/day
		Fludrocortisone (Florinef R)	All age children	0.025-0.2 mg/day

* If intravenous line is difficult to place, hydrocortisone sodium succinate can be intramuscularly injected (hydrocortisone sodium phosphate is allowed to be only intravenously administered in Japan). ** Standard bolus dose, neonate and infancy 25-50 mg, childhood 50-100 mg, school-aged 100-150 mg.

Table 6 Glucocorticoid and Mineralocorticoid dosages for initial treatment and maintenance therapy in 21-hydroxylase deficiency

Dose		HC (mg/m^2/day, 3 times a day)	FC * (mg/day, 2-3 times a day)	Sodium chloride * (g/kg/day, 3-8 times a day)
Initial treatment	Neonatal stage	25-100 **	0.025-0.2	0.1-0.2
Maintenance therapy	Neonatal stage Infant stage	10-20	0.025-0.2	0.1-0.2
	Preschool child stage Schoolchild stage Pubertal stage	10-15	0.025-0.2	
	Adult stage	10-15	0.025-0.2	

* FC (fludrocortisones) and sodium chloride are almost always required for classical salt-wasting form of 21-OHD. The doses of FC and sodium chloride are chosen based on serum sodium and potassium levels, plasma renin activity or concentration, and body weight gain. ** The dose is managed based on the severity of clinical symptoms. If adrenal crisis is suspected, a bolus intravenous injection of HC (50 mg/m^2) should be performed immediately. (Cited from ref 76. Partially modified)

III-3.3 Treatment of non-classical (NC) type 21-OHD

(1) In the asymptomatic NC type, we suggest no need for treatment.

(2) In the NC type, when clinical signs such as accelerated bone age and virilization due to androgen excess are observed, we recommend starting maintenance therapy as for the classical type (Table 6).

III-3.4 GC dose in stress or sickness *etc.* in 21-OHD

(1) When patients suffer from febrile illness (>38.5°C), gastroenteritis with dehydration or undergo operations under general anesthesia, we recommend increasing the GC dose according to the degree of each stress. *The corresponding amounts of GC for various type of stress are shown in Table 7.

(2) We suggest no need or little need of increase the GC dose in cases of emotional stress, very mild disease or light exercise.

(3) We highly recommend patients to carry emergency cards.

III-3.5 Monitoring of therapy in the growing period of 21-OHD

(1) We recommend evaluating height, body weight and blood pressure every 1 to 3 months and bone age annually after 1 year of age.

(2) We recommend periodic endocrinological examinations under constant conditions, such as fasting and no medication in the morning.

(3) We recommend taking care in patients with a Cushingoid appearance not to prescribe GC doses that are too high.

III-3.6 Therapy in adult 21-OHD

(1) In adult 21-OHD, we suggest that HC (Table 6) or a long-acting formulation of GC might be used.

(2) We recommend endocrinological examinations under the constant conditions, such as fasting and no medication in the morning, at least 2 times/year.

(3) We suggest that a serum 17-hydroxyprogesterone (17-OHP) level of 400–1,200 ng/dL may be useful as a way of monitoring optimal GC treatment.

(4) We recommend taking care in patients with a Cushingoid appearance not to prescribe GC doses that are too high, nor to use GC long term. In patients with Cushingoid features, we recommend investigating metabolic abnormalities and bone mineral density.

III-3.7 Treatment of Acute AI (adrenal crisis) in childhood

As a typical example, we suggest the following treatment in acute AI in childhood.

(1) In the first 1 h, perform a drip infusion of saline containing 5% glucose at the rate of 450 mL/m^2 or 20 mL/kg. Then, continue a drip infusion of the same solution for 24 h at the rate of 3,200 mL/m^2 [77].

(2) After the start of the above infusion, perform the rapid intravenous injection of 50–75 mg/m^2 HC

(3) When you cannot take an intravenous route, perform an intramuscular injection of HC succinate without delay.

(4) Thereafter, continuously administer 50–75 mg/m^2/day HC by drip infusion or administer 1/4 of the total amount every 6 h until hypovolemic shock has improved [77].

(5) After improvement of symptoms, switch to oral

Table 7 Stress dosing in 21-hydroxylase deficiency

Physical stress	Conditions	HC dose
Mild	Vaccination Upper respiratory infection up to low-grade fever	Maintenance dose
Moderate *	Infection associated with high fever (>38.5°C) Vomiting, diarrhea, poor feeding, sluggishness Minor surgery, trauma, dental treatment, burn	3- to 4-fold maintenance dose or 50-100 mg/m^2/day **
Severe *	Sepsis, major surgery	100 mg/m^2/day **

* If adrenal crisis is suspected, prior to surgery under general anesthesia or stress is difficult to control orally, a parenteral bolus administration of HC 50 mg/m^2 (infant: 25 mg, child: 50 mg; adult: 100 mg) is first performed. If intravenous line is difficult to place, hydrocortisone sodium succinate can be intramuscularly injected (hydrocortisone sodium phosphate is allowed to be only intravenously administered in Japan). ** For intravenous injection, continuous administration is preferable to bolus injection at 6-hour intervals. (Cited from ref 76)

medication and taper to maintenance doses over a period of about 1–4 weeks. In the acute phase, usually there is no need to use MC, because HC has a sodium retention effect.

*The recommended doses of HC in acute AI in children, neonate, infancy, childhoos and school-aged are shown in Table 5.

Supplementary comments and evidence
[Epidemiology]

In Japan, from 2003 to 2007, 1,935 children were estimated to have primary AI [78]. A study from Canada reported that in patients with primary AI of less than 18 years of age, 72% of cases were caused by congenital adrenal hyperplasia [79]. Primary AI by autoimmunity was observed in 13% of patients and other causal disorders, such as adrenoleukodystrophy, Wolman disease and unknown etiology were seen in the rest of the patients (15%).

Rates of mortality three to four times those in healthy individuals have been reported in patients with AI in the UK, Canada and USA [80-82]. In these patients, 12–25% of deaths were caused by hypoglycemia or AI itself. A report from the USA showed that 24% of deaths were sudden deaths or deaths with unknown etiology and among them, 74% of patients had combined pituitary hormone deficiency [82]. Rates of mortality ten times those in healthy children have been observed in children of less than 2 years old with GH deficiency and hypoglycemia. The mortality rate was 1/31–54 in children less than 6 years old with a history of hypoglycemia, and a mortality rate of 1/113–173 has been recorded in patients over 6 years old.

[Symptoms]

Vomiting, poor suckling, dehydration and weakness are common symptoms of acute AI during infancy. Abdominal pain, weakness, fatigue and mental disorders are observed in juvenile patients. Shock and hypoglycemic attack can happen at any age. Pigmentation is an important sign of AI, but it is observed only in primary AI, not in secondary AI. A history of present illness is quite informative for suspecting AI. AI should be suspected in patients with a history of treatment of congenital adrenal hyperplasia, a family history of adrenal disease, a history of labor-associated trauma and a history of autoimmune disorder. Iatrogenic AI is the most common cause of secondary AI, and a history of GC therapy should be sought in patients with aller-gic disease.

If appropriate diagnosis and treatment are given before the manifestation of AI, its prognosis is generally favorable. However, it can be fatal without appropriate treatment. Many reports describe that AI was first diagnosed by sudden death or sudden infant death syndrome. After initial therapy is successfully undertaken, long-term prognosis varies individually, depending on the causative disease of AI.

[Growth retardation and therapy monitoring in 21OHD]

There is no firm evidence concerning the optimal GC dose in infancy in the classical type of 21-OHD. In Western countries, low-dose HC (10–15 mg/m^2/day, or a maximum of 25 mg/m^2/day) has been proposed [74, 83]. In this HC dose range, suppression of adrenal androgens is insufficient, but does not substantially negatively affect growth at 3 years of age [84]. New Japanese guideline recommends 25-100 mg/m^2/day of HC in the initial dose. The dose is managed based on the severity of clinical symptoms.

HC (Cortril®) should be used as a maintenance therapy during the growth period because the short half-life of HC reduces the risk of growth retardation, compared with long-acting GC. Anti-growth action relative to HC has been reported to be 15 times stronger with prednisolone [85], and 70–80 times stronger with dexamethasone [86]. These long-acting GCs should be avoided in GC replacement in the growth period. Cortisone acetate is also not recommended for GC supplementation because enzymatic activity of 11β-HSD1 is relatively low in infancy and varies individually [87]. As to the optimal dose of HC for the prevention of growth retardation, no clear-cut data has been shown. It has been reported that when HC dose exceeds 15–17 mg/m^2/day adult height decreases [88]. As a monitoring hormone in 21OHD, 17-OHP is usually measured. The target concentration of serum 17-OHP during GC therapy has been shown to be 400–1,200 ng/dL in both children and adults [89], or <590 ng/mL [84] or 100–1,200 ng/dL in adolescents [90], but the target should be individualized. Complete normalization of serum 17-OHP usually suggests doses of GC that are too high. As another method of monitoring, a urine concentration of pregnantriol (a urine metabolite of 17-OHP) of 1.2–2.1 mg/m^2/day has been proposed [91]. In adult patients with 21-OHD who no longer have the problem of growth retardation, various types of GC have

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