

SFE/SFEDP adrenal insufficiency French consensus: Introduction and handbook

Consensus sur l'insuffisance surrénale de la SFE/SFEDP : introduction et guide

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Abstract

The French endocrinology society (SFE) and the French pediatric endocrinology society (SFEDP) have drawn up recommendations for the management of primary and secondary adrenal insufficiency in the adult and child, based on an analysis of the literature by 19 experts in 6 work-groups. A diagnosis of adrenal insufficiency should be suspected in the presence of a number of non-specific symptoms except hyperpigmentation which is observed in primary adrenal insufficiency. Diagnosis rely on plasma cortisol and ACTH measurement at 8am and/or the cortisol increase after synacthen administration. When there is a persistant doubt of secondary adrenal insufficiency, insulin hypoglycemia test should be carried out in adults, adolescents and children older than 2 years. For determining the cause of primary adrenal insufficiency, measurement of anti-21-hydroxylase antibodies is the initial testing. An adrenal CT scan should be performed if auto-antibody tests are negative, then assay for very long

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chain fatty acids is recommended in young males. In children, a genetic anomaly is generally found, most often congenital adrenal hyperplasia. In the case of isolated corticotropin (ACTH) insufficiency, it is recommended to first eliminate corticosteroid-induced adrenal insufficiency, then perform an hypothalamic-pituitary MRI. Acute adrenal insufficiency is a serious condition, a gastrointestinal infection being the most frequently reported initiating factor. After blood sampling for cortisol and ACTH assay, treatment should be commenced by parenteral hydrocortisone hemisuccinate together with the correction of hypoglycemia and hypovolemia. Prevention of acute adrenal crisis requires an education of the patient and/or parent in the case of pediatric patients and the development of educational programs. Treatment of adrenal insufficiency is based on the use of hydrocortisone given at the lowest possible dose, administered several times per day. Mineralocorticoid replacement is often necessary for primary adrenal insufficiency but not for corticotroph deficiency. Androgen replacement by DHEA may be offered in certain conditions. Monitoring is based on the detection of signs of under- and over-dosage and on the diagnosis of associated auto-immune disorders.

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Keywords: Consensus; Adrenal insufficiency; Primary and secondary; Adults and children

Résumé

La Société française d'endocrinologie (SFE) et la Société française d'endocrinologie pédiatrique (SFEDP) ont élaboré des recommandations sur la prise en charge de l'insuffisance surrénale primaire et secondaire de l'adulte et de l'enfant, à partir d'une analyse de la littérature réalisée par 19 experts répartis en 6 groupes de travail. Le diagnostic d'insuffisance surrénale doit être évoqué devant l'association de signes cliniques et biologiques non spécifiques, en dehors de la mélanodermie observée dans l'insuffisance surrénale primaire. Le diagnostic repose sur les dosages du cortisol et de l'ACTH le matin et/ou le dosage du cortisol après stimulation par l'ACTH synthétique (synacthène). En cas de doute, le test d'hypoglycémie insulinique est le test de référence chez l'adulte l'adolescent et l'enfant de plus de 2 ans. La recherche étiologique est basée sur le dosage en 1^{re} intention des anticorps anti 21-hydroxylase. En cas de négativité, un scanner surrénalien sera réalisé, puis le dosage des acides gras à chaînes longues sera effectué chez le garçon. Chez l'enfant, une cause génétique sera recherchée, principalement l'hyperplasie congénitale des surrénales. Devant un déficit corticotrope, après la recherche d'une prise prolongée de glucocorticoïdes sera effectuée une imagerie hypothalamo-hypophysaire. L'insuffisance surrénale aiguë est une complication grave souvent déclenchée par une infection gastro-intestinale. Elle nécessite après prélèvement pour dosage du cortisol et ACTH l'administration parentérale d'hémisuccinate d'hydrocortisone et la correction de l'hypovolémie et/ou de l'hypoglycémie. Sa prévention repose sur l'éducation thérapeutique du patient pour laquelle des programmes seront développés. Le traitement de l'insuffisance surrénale s'appuie sur la prise pluriquotidienne d'hydrocortisone à la dose la plus faible possible. La substitution minéralocorticoïde est réalisée en cas d'insuffisance surrénale primaire mais n'est pas nécessaire en cas d'insuffisance surrénale secondaire. La substitution androgénique par la DHEA peut être proposée dans certaines indications précises. La monitoring comportera la recherche de signes cliniques et biologiques de sous/surdosage et de maladies auto-immunes associées.

Mots clés : Consensus ; Insuffisance surrénale ; Primaire et secondaire ; Adultes et enfants

1. Introduction

The French endocrinology society (SFE) and the French pediatric endocrinology society (DFSDP) have drawn up recommendations for the management of primary and secondary adrenal insufficiency in the adult and child, based on an analysis of the literature by 19 experts participating to 6 work-packages. The fields which are covered by the consensus on adrenal insufficiency include epidemiology, screening methods and confirmation of diagnosis, strategies for identifying the cause, replacement therapy, acute adrenal insufficiency, monitoring of patients and patient's education. The strength of the recommendations was graded as strong when using the phrase "we recommend" or weak when using the phrase "we suggest". Quality of the evidence of recommendations was graded such as + denotes very low quality of evidence, ++, low quality; +++, moderate quality and +++, high quality. The manuscripts were reviewed by independent French experts.

2. Handbook

2.1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality [1]

The prevalence of primary adrenal insufficiency is estimated at between 82–144/million, with auto-immunity being the most common cause in adults and genetic causes, especially enzyme defects, being the most common cause in children. The prevalence of secondary adrenal deficiency is estimated to be between 150–280/million. The most frequent occurrence is believed to be corticosteroid-induced insufficiency, despite the incidence of clinically relevant deficiency after cessation of glucocorticoid treatment being widely debated. Data on mortality in adrenal insufficiency are contradictory, with studies from Sweden suggesting a two-fold increase in comparison to the general population, but this is not consistently reported in all studies. However, increased mortality has been consistently reported in young patients, associated with infection and/or acute adrenal

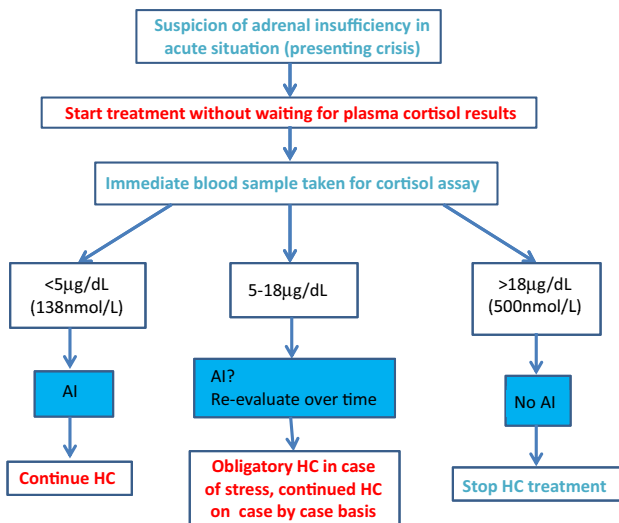


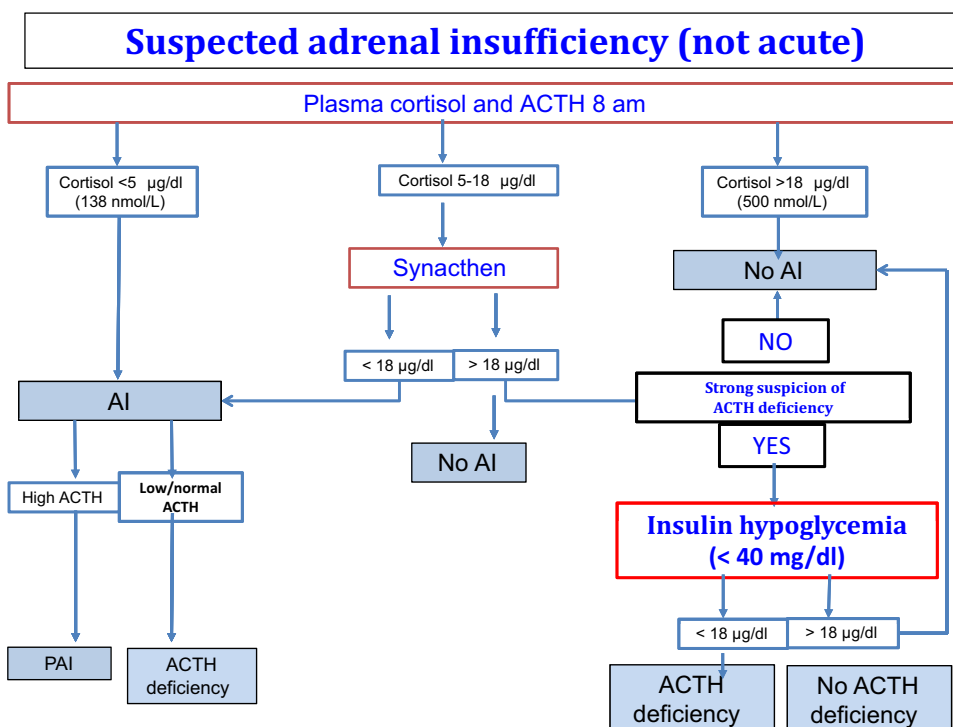
Fig. 1. Algorithm for exploring the hypothalamic pituitary adrenal axis in acute situations.

insufficiency. Acute adrenal deficiency (adrenal crisis) occurs in primary as well as secondary adrenal insufficiency. Its incidence, mostly determined in retrospective studies, is estimated in Europe at 6-8/100 patients/year. A prospective study reported 0.5 deaths/100 patient-years from adrenal crisis. Long-term morbidity of adrenal insufficiency is not well-established, the increased cardiovascular risk or bone demineralization which are not consistently reported may also be due to a supraphysiological glucocorticoid replacement therapy. However, alteration in quality of life, both in physical and mental health components,

has been demonstrated by several studies in both primary and secondary adrenal insufficiency.

2.2. Screening methods and confirmation of diagnosis [2]

A diagnosis of adrenal insufficiency should be suspected in the presence of a number of non-specific symptoms (fatigue, anorexia, weight loss, hypotension, hyponatremia and hyperkalemia amongst adrenal causes of insufficiency). The diagnosis should be considered in case of pituitary disease or a state of shock. Treatment should be commenced immediately without waiting for confirmation from biochemical tests, which rely on cortisol level at 8 am (expected to be lower) and on ACTH level (that is expected to be high in the case of primary adrenal insufficiency). If these tests are inconclusive, a Synacthen test should be carried out. The threshold limits are provided as a guide (Fig. 1). Low plasma cortisol and normal to low plasma ACTH indicates a pituitary origin for the deficiency. In this situation, the Synacthen test can give a false normal result, and if adrenal insufficiency is strongly suspected, an insulin hypoglycemia test or a metyrapone (Metopirone) test should be carried out in non acute situations (Fig. 2). In children younger than 2 years, hypoglycemia, dehydration and convulsions are frequently observed and in young girls, virilization is suspect of adrenal insufficiency. The circadian rhythm of cortisol is not present until after 4 months of age and the Synacthen test is the only one that is feasible. In children older than 2 years, the signs and diagnosis methods are the same as in the adult. Cessation of corticosteroid treatment is a frequent circumstance however there is little published data and no evidence for definitive guidelines. After ceasing a short period of corticosteroid treatment, patient



education is all that is required. After longer treatment, consensus leaves the choice up to the physician, between educating the patient and prescribing hydrocortisone in case of stress, or prescribing low daily dose hydrocortisone and evaluating the ACTH axis over time until normal function is recovered.

R2-1: a diagnosis of primary adrenal insufficiency (PAI) should be suspected in cases of:

- asthenia, weight loss, dehydration, hypotension, fever, abdominal pains, nausea and hyperpigmentation;
- patients at high risk of PAI (type 1 diabetes, auto-immune dysthyroidism, bilateral adrenal metastases);
- patients in an “acute” context: unexplained collapse, hypotension, vomiting or diarrhea;
- strong recommendation. Level of evidence: +++.

R2-2: a diagnosis of ACTH insufficiency should be suspected in the case of symptoms that suggest primary adrenal insufficiency (fatigue, hypotension, nausea, vomiting), with the exception of hyperpigmentation.

Strong recommendation. Level of evidence ++.

R2-3: diagnosis of ACTH insufficiency should also be systematically examined, even in patient with few or no symptoms, in patients with hypothalamic-pituitary disorders: tumors, inflammatory disease or infiltrative disease, surgery in this region, cranial trauma or radiotherapy. This diagnosis can be re-examined at regular intervals.

Strong recommendation. Level of evidence ++.

R2-4: replacement therapy should be started in ACTH insufficiency as a consequence of surgical treatment for Cushing’s syndrome or surgery for a cortisol secreting adrenal tumor. Hydrocortisone treatment in this case should be commenced in the perioperative period, before confirming or eliminating the diagnosis at a later time.

Strong recommendation. Level of evidence: +++.

R2-5: in the newborn and baby, we recommend examination for (i) primary adrenal insufficiency when patients present with abnormal external genitalia, episodes of hypoglycemia, neonatal cholestatic jaundice, loss of weight, dehydration; (ii) ACTH deficiency when patients present with midline defects, micropenis, cryptorchidism, episodes of hypoglycemia, neonatal cholestatic jaundice.

Strong recommendation. Level of evidence: +++.

R2-6: in older children and adolescents, we recommend examination for primary adrenal insufficiency or ACTH insufficiency in patients who present with the same signs as adult patients (R2-1, R2-2, R2-3) or with clinical signs of hyperandrogenism to screen for a pure virilizing form of congenital adrenal hyperplasia.

Strong recommendation. Level of evidence: +++.

R2-7: primary adrenal insufficiency should be considered in patients presenting with hyponatremia, hyperkalemia or unexplained episodes of fasting hypoglycemia.

Strong recommendation. Level of evidence: +++.

R2-8: ACTH insufficiency should be suspected in patients presenting with hyponatremia or episodes of unexplained hypoglycemia. Hyperkalemia is not included in the manifestations of ACTH insufficiency.

Strong recommendation. Level of evidence: +++.

R2-9: in acute or emergency situations, a cortisol concentration below 500 nmol/L (18 µg/dL) should be indicative of adrenal insufficiency and therefore hydrocortisone replacement should be commenced.

Strong recommendation. Expert opinion.

R2-10: replacement therapy for primary adrenal insufficiency or ACTH insufficiency must be commenced as soon as the diagnosis is suspected and continued until the diagnosis is confirmed or excluded.

Strong recommendation. Level of evidence +++.

R2-11: replacement therapy for ACTH insufficiency should be initiated in the case of surgical treatment for Cushing's syndrome or for an adrenal tumor secreting cortisol, with the treatment started in the perioperative period before later confirmation or exclusion of the diagnosis.

Strong recommendation. Level of evidence: +++.

R2-12: the diagnosis of primary adrenal insufficiency rests on evidence of low basal plasma cortisol levels and/or low cortisol levels in a stimulation test, and an elevated level of ACTH (see R2-17, R2-21, R2-25).

Strong recommendation. Level of evidence: +++.

R2-13: after establishing a diagnosis of primary adrenal insufficiency, we recommend that patients are examined for mineralocorticoid deficiency by assays for plasma renin (elevated) and aldosterone (low).

Strong recommendation. Level of evidence: ++.

R2-14: diagnosis of ACTH insufficiency relies on evidence of low cortisol in the basal state and/or during a stimulation test, and an ACTH level that is not elevated and thus not adapted to the low level of cortisol.

Strong recommendation. Level of evidence: +++.

R2-15: certain clinical situations cause elevated cortisol levels: estrogen administration, pregnancy and all acute intercurrent diseases. In these situations, diagnosis must rest on higher threshold levels of cortisol and/or on a group of assumptions (case history, ACTH and renin levels).

Strong recommendation. Level of evidence: +++.

R2-16: assay for urinary free cortisol should not be used in the diagnosis of adrenal insufficiency.

Strong recommendation. Level of evidence: +++.

R2-17: the disparity in cortisol measured by different kits/assay methods makes it impossible to define universal threshold values. Nevertheless, guidelines can be proposed for morning cortisol levels measured at 7–8 am:

- levels above 18 µg/dL (500 nmol/L) make the diagnosis of adrenal insufficiency unlikely;
- levels less than 5 µg/dL (138 nmol/L) make the diagnosis of adrenal insufficiency very likely;
- in the intermediate zone, between 5 and 18 µg/dL (138–500 nmol/L), it is necessary to perform a stimulation test.

Weak recommendation. Expert opinion.

R2-18: in babies, the absence of circadian rhythm for cortisol secretion in the first months of life means that baseline cortisol assays need to be repeated and treatment needs to be commenced based on probability of adrenal insufficiency (if cortisol level is low), and that a later Synacthen test will be required.

Weak recommendation. Level of evidence: ++.

R2-19: a Synacthen test can be performed (i) as first line testing or (ii) as second line testing after basal cortisol measurement, where basal cortisol levels neither confirm nor rule out adrenal insufficiency.

Strong recommendation. Level of evidence: ++.

R2-20: the Synacthen test normally uses 250 µg of Synacthen (or 125 µg in children under 2 years). To increase its sensitivity, a Synacthen test using a lower dose (1 µg) was developed. The comparative performance of the 1 µg dose to the classic test are controversial. Furthermore, the 1 µg dose is not commercially distributed and needs to be prepared at the time by the user, which poses both methodological and regulatory problems. Overall, the available comparative studies do not clearly show superiority of the 1 µg test over the 250 µg test.

Level of evidence: +++.

R2-21: if the Synacthen test shows an insufficient stimulation of cortisol, that is a level lower than 18 µg/dL (500 nmol/L) measured 30 or 60 min after injection, the diagnosis of adrenal insufficiency can be accepted and it is not necessary to perform further tests.

Weak recommendation. Level of evidence: +.

R2-22: the Synacthen test can give false normal results in situations where ACTH insufficiency is recent (<4 weeks after pituitary surgery, cranial trauma) or in the case of partial ACTH insufficiency. If the Synacthen test is normal but clinical signs suggest ACTH insufficiency and/or the clinical situation necessitates certainty regarding the ACTH axis (where other anterior pituitary deficiencies are identified), we recommend performing an insulin hypoglycemia or metopirone test.

Strong recommendation. Level of evidence: ++.

R2-23: insulin hypoglycemia is the reference test for confirming or excluding ACTH insufficiency in adults and in older children. It is recommended to perform the test if basal cortisol levels are in the intermediate zone, when the

Synacthen test is normal but clinical signs are suggestive of ACTH insufficiency or where diagnostic certainty is required. The insulin hypoglycemia test can also be done at the same time as examination of the somatotropin axis, where this is required.

Strong recommendation. Level of evidence: ++.

R2-24: insulin hypoglycemia test should be performed in a specialized hospital setting. It is contra-indicated in cases of seizures, coronary artery disease, where there is a history of stroke or in advanced age. In pediatric patients, it is contra-indicated in babies and very small infants.

Strong recommendation. Level of evidence: +++.

R2-25: a peak of cortisol > 18 µg/dL (500 nmol/L) (or above the threshold defined by the laboratory) after insulin hypoglycemia where blood glucose reached < 0.40 g/L (2.2 mmol/L) leads to exclusion of ACTH insufficiency.

Strong recommendation. Level of evidence: ++.

R2-26: the Metopirone test (short protocol) or the CRH test can be employed where an insulin hypoglycemia test is contra-indicated.

Weak recommendation. Level of evidence: ++.

R2-27: in case of continued doubt regarding possible latent ACTH insufficiency, we recommend that patients be educated on the prevention of ACTH insufficiency in acute situations, are given a prescription for hydrocortisone (oral and/or injectable) to use in case of intercurrent conditions.

Weak recommendation. Expert opinion.

R2-28: in adults, no monitoring is required after undergoing corticosteroid treatment of short duration (less than 3 weeks).

Weak recommendation. Expert opinion.

R2-29: in adults, information on warning signs and alerting of physicians involved in the patient's care is sufficient where corticosteroid treatment was for less than 3 months. In the absence of clinical signs, no assays are recommended.

Weak recommendation. Expert opinion.

R2-30: in adults, after treatments longer than 3 months, individual cases need to be carefully considered based on the duration of treatment, the cumulative dose, the presence of signs of hypercortisolism and/or symptoms that are suggestive of adrenal insufficiency (particularly asthenia). Patient education needs to be provided and their physicians need to be informed.

Weak recommendation. Expert opinion.

R2-31: in adult patients, two options are suggested, without sufficient evidence being available to recommend one approach over the other:

- systematic prescription of hydrocortisone, 10–15 mg/day (8–10 mg/m²/day) taken in 1–2 doses, until the restoration of cortisol secretion, or;
- patient education and prescription of hydrocortisone to be taken only in case of stress.

Weak recommendation. Expert opinion.

R2-32: evaluation of ACTH function should be performed in parallel—assay of cortisol at 8 am and in cases where the result is borderline after Synacthen stimulation, in general after cessation of treatment with synthetic corticosteroid with the aim of screening for patients who will benefit from continued replacement therapy with hydrocortisone. In case of known ACTH deficiency, assay of basal cortisol at 8 am (alternatively after Synacthen) can be repeated at regular intervals (every 3–6 months) until recovery of normal ACTH function.

Weak recommendation. Expert opinion.

R2-33: in children, in the absence of data that predict the occurrence and duration of adrenal insufficiency after corticosteroid therapy and in view of the existence of severe forms of acute adrenal insufficiency, the following approach is suggested:

- in cases of corticosteroid treatment of less than 3-week duration, it is not necessary to prescribe a switch to hydrocortisone treatment, except in cases where there is a high risk of acute adrenal insufficiency (severe infection, surgery) likely to occur in the days-weeks following cessation of corticosteroid treatment. In this situation, we suggest treatment with hydrocortisone (dose used in stress situations) and re-evaluation of ACTH function at a later time;
- in cases of corticosteroid treatment of more than three weeks duration, we suggest patient education and education of the parents on the signs of acute adrenal insufficiency, alerting of the physicians and evaluation of ACTH function (cortisol and ACTH at 8 am ± Synacthen test if the assay results are inconclusive).

Weak recommendation. Expert opinion.

R2-34: in children, two options can be suggested for cessation of corticosteroid therapy when the dose of corticosteroid reaches an equivalent prednisone dose of 3 mg/m²/day or less:

- either a systematic switch to hydrocortisone (8–10 mg/m²/day in children and 10–12 mg/m²/day in babies) taken in two doses until evaluation of ACTH function is performed, which would allow hydrocortisone treatment to be stopped when normal secretion of cortisol is returned (> 18 µg/dL or 500 nmol/L). It is not necessary to perform a Synacthen test if 8 am cortisol levels are < 5 µg/dL (or 138 nmol/L), or;
- a prescription for hydrocortisone uniquely in case of situations with a risk of acute adrenal insufficiency, only if 8 am cortisol values at cessation of corticosteroid treatment are higher than 5 µg/dL (138 nmol/L). ACTH function is then re-evaluated at regular intervals until recovery of normal function.

R2-35: the study group encourages endocrinologists to declare confirmed cases of clinical adrenal insufficiency, as a result of corticosteroid therapy, to pharmacovigilance authorities with a reminder that there is a legal obligation to report adverse effects as with any other drug.
Weak recommendation. Expert opinion.

2.3. Strategies for identifying the cause of adrenal insufficiency: diagnostic algorithms in adults and children (Figs. 3–5) (Tables 1 and 2) [3]

In the majority of cases in adults, primary adrenal insufficiency is of auto-immune origin. It is therefore recommended that a test for anti-21-hydroxylase antibodies be performed as part of initial testing. If the auto-immune origin is confirmed, in the case of clinical signs that are indicative of the possibility of other auto-immune disorders, it is recommended to then test for auto-immune polyendocrinopathy type 1 (APECED syndrome). An adrenal CT scan should be performed if auto-antibody tests are negative, or where other clinical signs suggest a rarer etiology but may require rapid commencement of patient care (tuberculosis, other infections, tumors, hemorrhage, etc.). In the case of negative results of the first two tests, assay for very long chain fatty acids is recommended in males, particularly in young subjects (Figs. 3 and 5 Table 1). In the case of isolated corticotropin (ACTH) insufficiency, in both adults and children, it is recommended to first eliminate iatrogenic origins for the disease (corticosteroid treatment-induced or after treatment for Cushing’s syndrome). If all of these etiologies are excluded, exploration of other pituitary axes by hypothalamic-pituitary MRI should be done (Table 2). In neonates, primary adrenal insufficiency or ACTH insufficiency is most often due

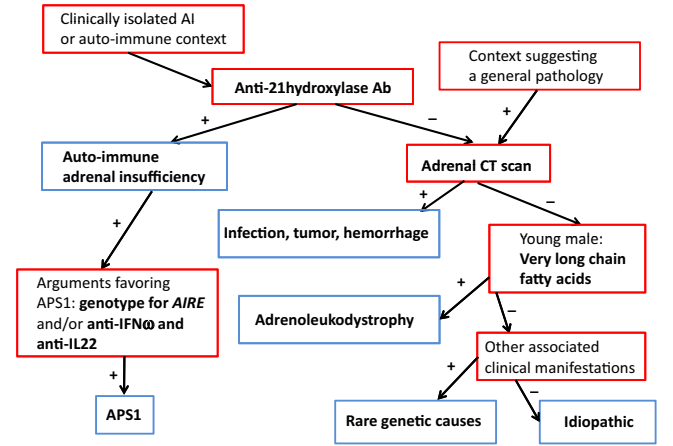


Fig. 3. Decision tree for diagnosing etiology of primary adrenal insufficiency in the adult.

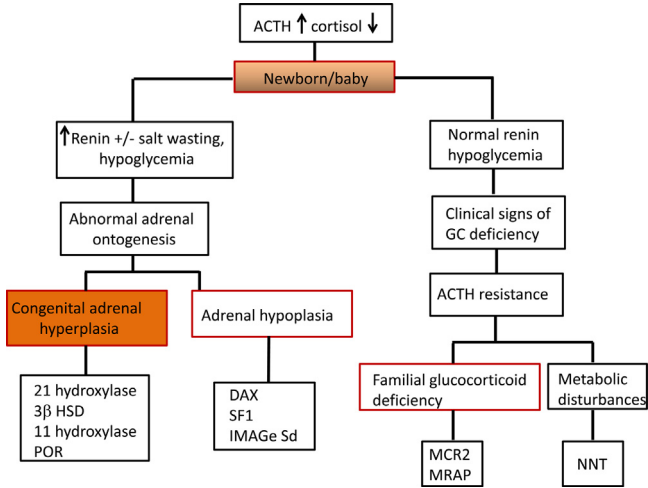


Fig. 4. Decision tree for diagnosing etiology of primary adrenal insufficiency in the new born and baby.

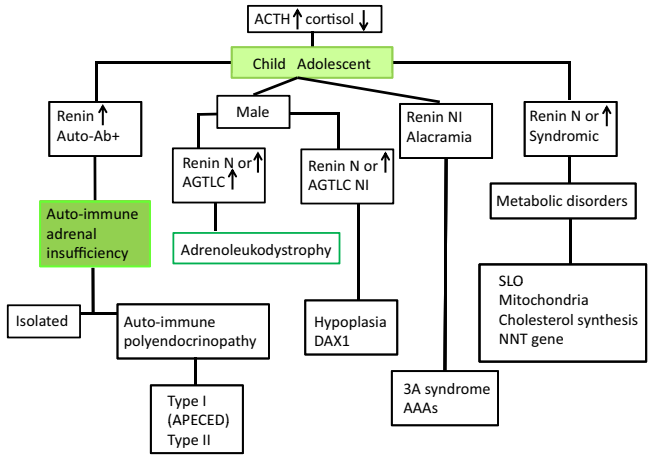


Fig. 5. Decision tree for diagnosing etiology of primary adrenal insufficiency in the child and adolescent.

to a genetic anomaly, with congenital adrenal hyperplasia being the principal etiology (Figs. 4 and 6 Table 3). In older children, testing for an auto-immune etiology is needed. In the case of negativity for auto-antibodies, depending on associated clinical signs, other genetic causes should be considered including adrenoleukodystrophy in boys (Fig. 6). In the case of congenital ACTH insufficiency, testing for other pituitary manifestations should be carried out to aid in further molecular analyses of genes that are implicated in pituitary development (Fig. 6).

R3-1: we recommend examination for the etiology of AI to optimise its management and to avoid overlooking causal pathologies that can be treated.
Strong recommendation. Expert opinion.

Table 1
Principal etiologies in adult primary adrenal insufficiency and their clinical characteristics.

Etiology	Origin	Clinical manifestations associated with adrenal insufficiency (in order of frequency)	Diagnostic criteria
<i>Auto-immune</i>			
APS1 (APECED)	Monogenic Mutations of <i>AIRE</i> gene Polygenic	Candidiasis (83–100%) Hypoparathyroidism (79–93%) AI (60–70%) Ovaritis (60%) Dental enamel hypoplasia (77%) Alopecia (29–37%) Keratitis (12–35%) Malabsorption (15–18%) Hepatitis (12–20%) Gastritis (13–15%) Vitiligo (12–13%) Thyroiditis (3–10%) Diabetes (type 1) (2–12%) Hypophysitis (7%) Interstitial nephritis, obliterative bronchiolitis, febrile cutaneous rash (more rare). . . Thyroiditis (65–75%) Diabetes type 1 (50–60%) AI (19–40%) Ovaritis (5–10%) Gastritis (5–29%)	At least 2 components of Whitaker triad (1 alone if siblings affected): candidiasis, AI with positive Ab anti-21- hydroxylase, hypoparathyroidism: sequencing of <i>AIRE</i> gene; anti-interferon- ω or anti-IL22 AB if available AI associated with other autoimmune pathologies, principally thyroiditis and/or type 1 diabetes Anti-21- hydroxylase Ab
APS2	HLA: class II: DR3-DQ2, DR4-DQ8, DRB1*0404 and *0301; class I: DR3-B8	Celiac disease (3–10%) Vitiligo (10–20%)	
Isolated auto-immune AI	Other molecules: linked to CMH: MICA, CIITA; co-stimulators of CMH: CTLA-4, PTPN22; linked to Ly B: FcRL3 promoter; innate immunity: CLEC16A, NALP1; vitamin D receptor. . .	Alopecia (2–6%) Hypoparathyroidism (3%) Hypophysitis (2%)	Anti-21- hydroxylase Ab Context of familial autoimmune pathologies
<i>Infectious</i>	Polygenic (cf APS2)		
Bacterial	Tuberculosis (Mycobacterial), <i>Haemophilus influenzae</i> , Syphilis (<i>Treponema pallidum</i>)	Other systemic manifestations of the pathology	Adrenal CT, IDR, <i>IGRA</i> , culture, PCR
Viral	HIV, CMV, HSV. . .		

Table 1
(Continued)

Etiology	Origin	Clinical manifestations associated with adrenal insufficiency (in order of frequency)	Diagnostic criteria
Parasitic	<i>Trypanosoma african (Trypanosoma brucei)</i>		
Fungal	<i>Pneumocystis carinii</i> , <i>histoplasmosis</i> , <i>cryptococcosis</i> , <i>coccidiomycosis</i> , <i>blastomycosis</i>	Opportunistic infections	
Hemorrhagic	Anticoagulants, inhibitor of tyrosine kinase (sunitib) Antiphospholipid antibody syndrome Meningococcal sepsis (Waterhouse-Friderichsen) Disseminated intravascular coagulation	Acute adrenal insufficiency	Adrenal CT (hemorrhage)
Post-surgical Bilateral adrenalectomy	Uncontrolled Cushing syndrome, bilateral adrenal masses, bilateral phaeochromocytoma		
Tumoral: secondary, rarely primary	Bilateral metastases pulmonary, renal, gastric, breast, colon, pancreatic, melanoma, lymphoma		CT
Infiltrative	Amylosis, hemochromatosis, sarcoidosis, xanthogranulomatosis		
Drug-related	Ketoconazole, fluconazole, etomidate, metyrapone Phenobarbital, phenytoin, rifampicine, Mitotane Anti-CTLA4 (ipilimumab) associated or not with anti-PD1 (nivolumab, pembrolizumab)	Inhibition of cytochrome P450-dependent enzymes (<i>CYP11A1</i> , <i>CYP11B1</i>) Induction of cytochrome P450-dependent enzymes (<i>CYP2B1</i> , <i>CYP2B2</i> , <i>CYP3A4</i>) increasing cortisol metabolism Cytotoxic mechanism Auto-immune mechanism	
Genetic (Table 3 pediatric)	Adrenoleukodystrophy (mutation of <i>ABCD1</i>)	Table 3, pediatric	

IGRA: interferon-γ release assay: QuantiFERON-Tb Gold in Tube[®] (Cellestis Ld. Carnegie, Victoria, Australia) or T-SPOT.TB[®] (Oxford Immunotec Ltd., Abingdon, UK).

Table 2
Etiologies of ACTH insufficiency in adults.

Etiology	Pathophysiological mechanisms	Clinical manifestations associated with adrenal insufficiency	Diagnostic criteria
<i>Iatrogenic</i>			
Post-corticosteroid, or post-treatment of Cushing's syndrome	Inhibition of ACTH axis	Isolated ACTH insufficiency	Context dependent
Opioids		Gonadotropin insufficiency	
Antidepressants (imipramine)	ACTH deficiency		
Antipsychotics (chlorpromazine)			
Hypophysitis iatrogenic:			
Interferon-ribavirine			
Anti-CTLA4 (ipilimumab) ± associated with anti-PD1 (nivolumab, pembrolizumab)		ACTH deficiency sometimes indicative Frequently associated with TSH deficiency ± gonadotropin, GH deficiency, rarely with diabetes insipidus or SIADH	
<i>Tumors</i>			
Hypothalamic: craniopharyngiomas, metastases (lung, breast)	CRH deficiency	Other anterior or posterior pituitary deficiencies, ± other clinical manifestations linked to the causal pathology	MRI, context dependent
Pituitary: macroadenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, carcinomas (rarely)	ACTH deficiency		
Pituitary surgery or radiotherapy (pituitary tumors, cerebral tumors, in the nasopharyngeal region, leukemias)	Deficiency in CRH and/or ACTH	Other anterior or posterior pituitary deficiencies	Context dependent
<i>Hypophysitis primary</i>			
Lymphocytic	Deficiency in CRH and/or ACTH	ACTH deficiency, sometimes isolated, ± diabetes insipidus and other anterior/posterior pituitary deficiencies, headache, vision problems, other associated auto-immune diseases	MRI, context dependent (females, peri-partum)
Granulomatous		Headache, vision problems, other anterior/posterior pituitary deficiencies	MRI, histology
Xanthomatous		Headache, vision problems, other anterior/posterior pituitary deficiencies, other systemic effects (retroperitoneal fibrosis, sialadenitis, dacryoadenitis, adenopathies, nephritis. . .)	MRI, histology, biopsy of target organ, IgG4 assay, context (males, mature age)
IgG4 hypophysitis (IgG4 fibro-sclerosing disease)			
<i>Hypophysitis</i>			
Secondary to systemic pathology: infectious: tuberculosis, syphilis, actinomycosis, meningitis, abscess; inflammatory: sarcoidosis, ANCA vasculitis, Wegener; infiltrative: hemochromatosis, amylosis, histiocytosis		Headache, visual problems, other anterior or posterior pituitary deficiencies, ± other clinical manifestations linked to the causal pathology	
<i>Vascular</i>			
Pituitary apoplexy	ACTH deficiency	Severe headaches, vision problems, nausea, vomiting, other anterior/posterior pituitary deficiencies	MRI
Sheehan syndrome		Hemorrhage in childbirth/delivery, headaches, vision problems, nausea, vomiting, other anterior/posterior pituitary deficiencies	MRI, context peri-partum
<i>Traumatic</i>			
Cranial trauma	CRH and/or ACTH deficiency (from pituitary hypoperfusion)	Other anterior/posterior pituitary deficiencies (often gonadotropin and GH)	Context dependent
Genetic (Fig. 3, pediatric)			

Adapted from Charmandari, 2014.

2.4. Replacement therapy for adrenal insufficiency [4]

Glucocorticoid replacement is mainly based in France on the use of hydrocortisone, that should be given at the lowest possi-

ble dose, in 2 or 3 intakes per day. Dose monitoring should be based on clinical signs of over or under-replacement: biological markers should not be used on a regular basis. Mineralocorticoid replacement is based on a mean dose of 100 micrograms of

Table 3
Etiologies of primary adrenal insufficiency in children.

Pathology	Gene	OMIM	Associated signs
<i>Abnormal steroidogenesis</i>			
Congenital adrenal lipoid hyperplasia	<i>Star</i>	201710	46,XY DSD, gonadal insufficiency
P450 side chain cleavage deficiency (P450sc)	<i>CYP11A1</i>	118485	46,XY DSD, gonadal insufficiency
3 β -hydroxysteroid dehydrogenase (CAH) deficiency	<i>HSD3B2</i>	201810	46,XY DSD and 46,XX DSD, gonadal insufficiency
21-hydroxylase deficiency (CAH)	<i>CYP21A2</i>	201910	46,XX DSD, hyperandrogenism
11 β -hydroxylase deficiency (CAH)	<i>CYP11B1</i>	202010	46,XX DSD, hypertension, hyperandrogenism
17-hydroxylase deficiency (CAH)	<i>CYP17A1</i>	202110	46,XY DSD, hypertension, gonadal insufficiency
P450 oxidoreductase deficiency (CAH)	<i>POR</i>	613571	46,XY DSD, 46,XX DSD, gonadal insufficiency Antley-Bixler syndrome (bone defects)
Aldosterone synthase Deficiency	<i>CYP11B2</i>	124080	Isolated mineralocorticoid deficiency
<i>Adrenal hypoplasia/dysgenesis</i>			
X-linked adrenal hypoplasia	<i>NROB1 (DAX1)</i>	300200	Hypogonadism hypogonadotropic
SF1 deficiency	<i>NR5A1 (SF1)</i>	184757	46,XY DSD, gonadal insufficiency
IMAGe syndrome	<i>CDKN1C</i>	614732	Intra-uterine growth retardation, bone defects, genital abnormalities, facial dysmorphia, hypercalcemia
MIRAGE syndrome	<i>SAMD9</i>	617053	Myelodysplasia, infection, growth retardation, genital abnormalities, enteropathy
Pallister-Hall syndrome	<i>GLI3</i>	165240	Hypothalamic hamartoma, polydactyly, bifid epiglottis, imperforate anus, genital abnormalities
Meckel syndrome	<i>MKS1</i>	249000	Polycystic kidney, cerebral malformations, occipital encephalocele, polydactyly, hepatic fibrosis
Pena-Shokeir syndrome	<i>DOK7 RAPSIN</i>	208150	Arthrogryposis, facial dysmorphia, intra-uterine growth retardation, camptodactyly, pulmonary hypoplasia, cardiac malformation, intestinal malrotation
<i>ACTH resistance</i>			
Familial glucocorticoid deficiency	<i>MC2R MRAP</i>	202200607398	Absence of mineralocorticoid deficiency, large size
Triple A syndrome (Allgrove syndrome)	<i>AAAS</i>	231550	Alacrimia, achalasia, deafness, neurological defects, hyperkeratosis
Oxidative stress defect DNA repair defect	<i>NNT TXNRD2 MCM4</i>	614736606448609981	Affected organs that are rich in mitochondria (myocardiopathy, hypothyroidism, partial GH deficiency) NK cell deficiency, recurrent viral infections, short stature, microcephaly
<i>Peroxisomal diseases</i>			
Adrenoleukodystrophy	<i>ABCD1</i>	300100	Progressive degenerative neurological damage, deafness, vision problems, convulsions, accumulation of very long chain fatty acids
Infantile Refsum disease	<i>PHYH, PEX7</i>	266500	Pigmentary retinopathy, deafness, cerebellar ataxia, hypotonia, growth retardation, intellectual disability
Zellweger syndrome	<i>PEX (PEX1)</i>	214100	Facial dysmorphia, severe hypotonia, epilepsy, severe intellectual disability, blindness, deafness, hepatomegaly, genital abnormalities
<i>Mitochondrial cytopathies</i>			
Kearns-Sayre syndrome	<i>Mitochondrial DNA deletion</i>	530000	Progressive ophtalmoplegia, deafness, cardiac abnormalities, ataxia, intellectual disability, myopathy, hormonal deficiencies, renal insufficiency
<i>Auto-immune diseases</i> (cf. Adult able)			
<i>Acquired pathologies</i> (cf Adult table)			

Adapted from Malikova, 2014.
DSD: disorders of sex development.

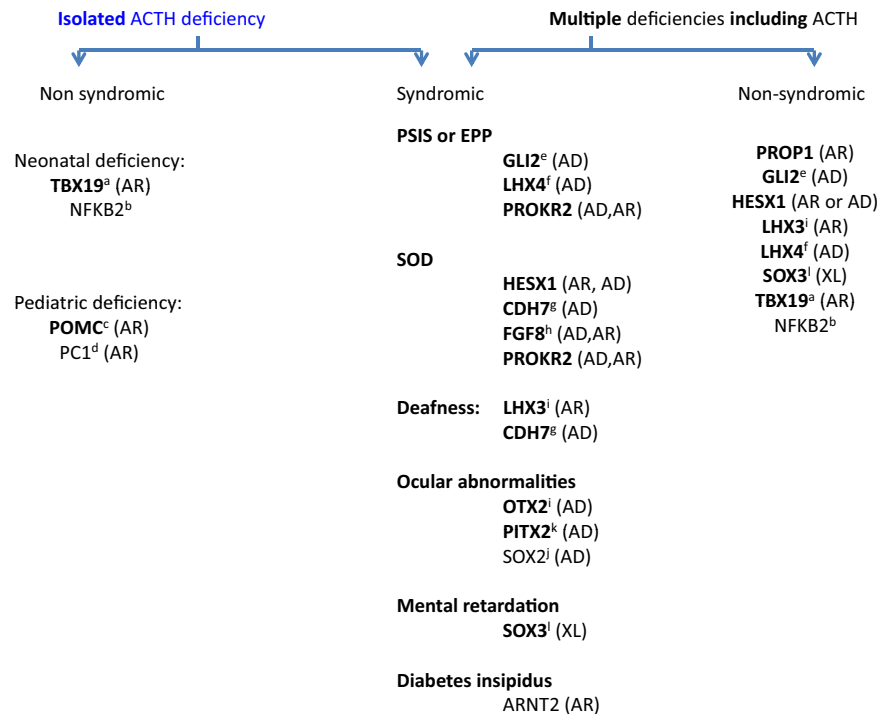


Fig. 6. Decision tree for congenital ACTH insufficiency in children. Legends: PSIS: pituitary stalk interruption syndrome; EPP: ectopic posterior pituitary; SOD: septo-optic dysplasia a: uniquely if neonatal complete +/- transitory GHD before age 2yrs; b: common variable immune deficiency, not present at birth; c: with obesity; d: with hypoglycemia +/- pigmentation problems; e: polydactyly or cleft palate/hare lip in siblings or family; f: Chiari malformation; g: sometimes Charge syndrome; h: if holoprosencephaly; i: sometimes abnormality in neck rotation; j: microphthalmia; k: Rieger syndrome; l: mental retardation.

R3-2: we recommend assay for anti-21-hydroxylase antibodies as first-line testing in adults
Strong recommendation, level of evidence ++.

R3-5: we suggest assays for either anti-interferon ω or anti-IL22 antibodies, if available, in those cases requiring a rapid diagnosis, i.e. those with serious visceral sequelae.
Weak recommendation. Expert opinion.

R3-3: we suggest that assay for anti-adrenal antibodies be discontinued.
Strong recommendation, level of evidence ++.

R3-6: in adult patients, we recommend adrenal CT when tests are negative for anti-21-hydroxylase antibodies or immediately in the case of clinical signs suggesting a general pathology that requires urgent management (tuberculosis, hemorrhage, tumor).
Strong recommendation, level of evidence ++.

R3-4: in young patients with auto-immune adrenal insufficiency, in case of clinical symptoms that are suggestive of auto-immune polyendocrinopathy 1 (APS1) – i.e. candidiasis and hypoparathyroidism, keratitis, alopecia, hypoplasia of dental enamel, malabsorption, ovaritis, hepatitis –, we recommend genotyping for the *AIRE* gene.
Strong recommendation, level of evidence +.

R3-7: if an auto-immune etiology is not found, and in the case of a normal adrenal CT, assay for very long chain fatty acids should be carried out, particularly in adolescent males but also in adult male subjects.
Weak recommendation. Expert opinion.

fludrocortisone, and free sodium intake. Primary adrenal insufficiency but not corticotroph deficiency should be replaced by fludrocortisone. Dose monitoring should be based on clinical signs of over and under-replacement, and the level of renin.

Finally, DHEA can be delivered to women with altered quality of life despite optimal glucocorticoid and mineralocorticoid

R3-8: in the case of isolated ACTH insufficiency at presentation, previous or current corticosteroid treatment, either by systemic or local administration, should be suspected.

Strong recommendation. Expert opinion.

R3-9: in the absence of previous corticosteroid treatment or previous management of Cushing's syndrome, ACTH insufficiency should be explored. This requires a complete examination of pituitary hormones and morphology (pituitary MRI in the absence of contraindication).

Strong recommendation. Expert opinion.

R3-10: in newborns and babies, in the case of glucocorticoid deficiency $\pm$ mineralocorticoid deficiency, we recommend examination for congenital adrenal hyperplasia by assays for adrenal steroids using LC-MS/MS. In the absence of evidence of enzyme deficiency, we recommend high-speed sequencing of a panel of genes responsible for other rare causes of adrenal insufficiency.

Strong recommendation, level of evidence ++.

R3-11: in newborns and babies, in the case of deficiency restricted to glucocorticoids, we recommend high-speed sequencing of the same panel of genes mentioned above (R3-10).

Strong recommendation, level of evidence ++.

R3-12: in children and adolescents, in the case of glucocorticoid and mineralocorticoid deficiency, we recommend as first-line testing for anti-21-hydroxylase antibodies. In the absence of antibodies, and in males, we recommend assay for very long chain fatty acids to confirm adrenoleukodystrophy. If all tests are negative, examination of *DAX-1* (*NROB1*) gene can be carried out prior to studying the panel of genes.

Strong recommendation, level of evidence ++.

R3-13: in children and adolescents, in the case of glucocorticoid deficiency $\pm$ mineralocorticoid deficiency, we recommend that in males examinations performed to confirm a diagnosis of adrenoleukodystrophy, and depending on associated clinical and biochemical signs, high-speed sequencing of the same panel of genes as mentioned above (R3-10) is carried out.

Strong recommendation, level of evidence ++.

R3-14: in the newborn, diagnosis of ACTH deficiency should be followed with a complete examination of the pituitary as well as examinations for cerebral, ocular and cardiac malformations.

Strong recommendation, level of evidence ++.

R3-15: in the newborn, diagnosis of ACTH deficiency associated with other pituitary deficiencies should be followed by genetic analyses which may be useful for an evolving prognosis. In the presence of mutation of *TBX19* gene and neonatal GH deficiency, other axes should be reevaluated around 2 years of age, to confirm reversal of the GH deficiency.

Strong recommendation. Expert opinion.

R3-16: in children and adolescents, diagnosis of multiple constitutional non-syndromic pituitary deficiencies should be followed by genetic testing in order to advise the family and a screening of family members if necessary.

Strong recommendation; Expert opinion.

R3-17: in children or adolescents, the presence of isolated ACTH deficiency should be followed by examination for immune deficiency and analysis of the *NFKB2* gene. If there is associated childhood obesity, testing for POMC gene anomaly should be performed.

Strong recommendation, level of evidence ++.

2.5. Acute adrenal insufficiency in adults and pediatric patients [5]

replacements. Dose monitoring should be based on plasma levels of DHEA and clinical benefits of the treatment.

Acute adrenal insufficiency is a serious condition with an estimated frequency of 6 to 8.3 episodes/100 patients/year.

R4-1: in adults and children, we recommend the use of hydrocortisone as first line treatment of primary or secondary adrenal insufficiency. The treatment is a lifetime treatment except in special cases such as recovery from surgery for hypercortisolism, or after stopping of glucocorticoid treatment.

Strong recommendation, level of evidence ++++.

R4-2: in adult patients, first generation long-acting glucocorticoids (prednisolone, dexamethasone) should not be used except in the case of poor efficacy of hydrocortisone due to its pharmacokinetics. In children, they should not be used except on specialist advice.

Weak recommendation, level of evidence ++.

R4-3: in the adult patient, we recommend the lowest possible replacement dose of hydrocortisone that is tolerated to treat adrenal insufficiency, keeping in mind that a dose of 15–25 mg/day is used as replacement in primary adrenal insufficiency (Addison's disease). (We recommend a lower dose [10–20 mg/day] to substitute for corticotroph deficiency). In children, for primary adrenal insufficiency due to CAH, we recommend a dose of hydrocortisone of 10–18 mg/m²/day, higher in the neonatal period (20–40 mg/m²/day during the first month) and in other cases of primary adrenal insufficiency a dose of 8–15 mg/m²/day.

We recommend a lower dose (8–10 mg/m²/day) in the case of corticotroph deficiency, with the highest dose in babies prior to weaning.

Strong recommendation, level of evidence +++.

R4-4: in adults and children, we suggest that the dose of hydrocortisone is splitted into 2 or 3 administrations per day, with the highest dose in the morning. A regimen of 3 doses is recommended in babies and young children.

Weak recommendation, level of evidence ++.

Infection, particularly gastrointestinal infection, is the most frequently reported initiating factor in adults and children but there are multiple other etiologies. Diagnosis is through clinical signs, supported by standard biochemical examinations once adrenal insufficiency is confirmed. Diagnosis can be difficult if the defi-

R4-5: in adults, we do not recommend the use of prolonged release hydrocortisone or hydrocortisone delivered by subcutaneous pump. In children, we do not recommend glucocorticoids other than hydrocortisone, nor hydrocortisone in suspension.

Weak recommendation: expert opinion.

R4-6: in adults, we recommend monitoring of treatment based on clinical signs of overdose or under-dosage. We do not recommend routine use of biochemical markers for adjustment of replacement therapy. In children, we recommend clinical monitoring (growth, puberty) and observation of clinical signs of overdose and under-dosage. We do not recommend routine use of biochemical markers for adjustment of replacement therapy, except in the case of congenital adrenal hyperplasia, where we recommend regular assay of biochemical markers (see National guidelines for diagnosis and treatment of congenital adrenal hyperplasia, [PNDS] 2011).

Strong recommendation, level of evidence +++.

R4-7: we suggest that around time of delivery, the dose of hydrocortisone should be increased and administered by IV drip in cases of digestive intolerance.

Weak recommendation, level of evidence ++.

ciency is partial or in the case of acute adrenal insufficiency that has just manifested. If acute adrenal insufficiency is suspected, blood samples should be taken and assayed immediately for cortisol and ACTH though treatment should be commenced without waiting for assay results. Treatment should be by parenteral hydrocortisone hemisuccinate, in adults at 100 mg IM or IV then continuous IV infusion at 100 mg/24 h (or via bolus delivered IV or IM at 6 h intervals). In children, 2 mg/kg each 6–8 h, IM or SC, or each 6 h via IV drip, depending on the clinical state. Correction of hypovolemia and hypoglycemia, particularly in children (using G5% or G10%), and the loss of electrolytes requires treatment as well as treatment of the cause of adrenal crisis. Clinical improvement after administration of hydrocortisone is the best diagnosis criterion. Ongoing treatment is then by oral administration of hydrocortisone, tripling the usual dose (at least 60 mg/24 h) splitted in three doses during the course of the day and then gradually reducing the dose over several days to arrive at the normal dose. In adult patients with primary adrenal insufficiency, treatment with fludrocortisone is recommended when the dose of hydrocortisone is less

R4-8: in adults, we recommend mineralocorticoid replacement using fludrocortisone at a mean dose of 100 µg/day (individually adjusted) and a free intake of dietary sodium in patients with primary adrenal insufficiency with mineralocorticoid deficiency. Patients with corticotroph insufficiency should not be treated with a mineralocorticoid component.

Strong recommendation, level of evidence +++.

In children, we recommend mineralocorticoid replacement using fludrocortisone at a dose of 50–100 µg/day. Oral administration of sodium (1–2 g/day) is necessary up to 1–2 years of age in children with primary adrenal insufficiency with mineralocorticoid deficiency. Children with corticotroph insufficiency should not be treated with mineralocorticoid replacement.

Strong recommendation, level of evidence ++.

R4-9: in adults, we recommend that monitoring and adjustment of mineralocorticoid replacement be based on clinical and biochemical signs of under-dosage (increased salt appetite, hypotension, nausea, hyponatremia, hyperkalemia, elevated renin) or of overdose (hypertension, edema, hypokalemia, undetectable or lower than normal renin).

Strong recommendation, level of evidence +++.

In children, we recommend monitoring and adjustment of mineralocorticoid replacement based, as in adult patients, on clinical and biochemical signs of under dosage and equally on particular monitoring of growth curves in young children. We recommend maintenance of plasma renin at values from normal to higher than normal levels.

Strong recommendation, level of evidence ++.

R4-10: we suggest that androgen replacement should be considered in women with primary or secondary adrenal insufficiency who are suffering from an alteration in quality of life, problems with mood and a loss of libido despite optimal glucocorticoid and mineralocorticoid replacement.

Weak recommendation, level of evidence ++

than 50 mg/day. In children, fludrocortisone can be reintroduced when oral hydrocortisone is being administered. Prevention of acute adrenal crisis requires the education of the patient and/or parent, in the case of pediatric patients, and their physician in

R4-11: the initial dose of DHEA for androgen replacement should be 25–50 mg/day over a period of 3 to 6 months, with adjustment of the dose as a function of (i) circulating levels of plasma DHEA during replacement treatment and (ii) the effects on symptoms identified prior to treatment. In the absence of a beneficial effect or in the case of adverse effects of androgen treatment, replacement therapy should be ceased.

Weak recommendation, level of evidence ++.

the following: normal dietary sodium intake, increasing the oral dose of medication in the case of illness, stress or intense activity and the delivery of injectable hydrocortisone hemisuccinate by family/carers or the patient themselves in an emergency as well as carrying a card identifying the patient as suffering from adrenal insufficiency.

2.5.1. Treatment of acute adrenal crisis

R5-1: in adults with an adrenal crisis, we recommend injection of hydrocortisone hemisuccinate 100 mg by IM or IV route followed immediately by IV infusion of 100 mg/24 h by syringe pump (alternatively, bolus injection IV or IM of 25 mg each 6 h). Treatment needs to be commenced urgently, after assay for cortisol and ACTH if the diagnosis of adrenal insufficiency was not previously known, and without waiting for results.

After correction of clinical and fluid balance problems, we recommend a return to oral administration of hydrocortisone, tripling the normal dose (at least 60 mg/24 h in patients normally treated with low dose), taken as 3 doses across the day (morning, midday and evening). Return to normal dose should then be by progressive reduction of the dose over several days.

Treatment with fludrocortisone should not be recommenced until the hydrocortisone dose is less than 50 mg/day.

Strong recommendation. Expert opinion.

2.5.2. Prevention of an adrenal crisis

2.6. Modalities and frequency of monitoring of patients with adrenal insufficiency. Patient education [6]

Patients with adrenal insufficiency require regular, specialised monitoring in order to optimise their replacement therapy, to detect signs of under- and over-dosage, and to examine for possible associated disorders (auto-immune disorders in the case of auto-immune primary adrenal insufficiency either isolated or as part of auto-immune polyendocrinopathy syn-

Table 4

Clinical manifestations and recommendations for surveillance of patients with adrenal insufficiency suffering from auto-immune polyendocrinopathy type 1 (PEA1 or APECED syndrome) (additional to specific surveillance of adrenal insufficiency detailed elsewhere).

Affected organ(s)	Frequency of occurrence	Age at occurrence	Initial tests, then repeated each 2–3 years, or sooner in case of clinical justification	Annual monitoring
Mucocutaneous manifestations				
Mucocutaneous candidiasis	83–100%	Childhood	Stomatological examination ± other specialist consultations, dermatology, ophthalmology if necessary	Stomatological examination ± other specialist consultations, dermatology, ophthalmology if necessary
Hypoplasia of dental enamel				
Alopecia	77%	Childhood		
Keratoconjunctivitis				
Vitiligo	29–37%	Childhood		
	12–35%	Childhood		
	12–13%	Childhood		
Endocrine manifestations				
Hypoparathyroidism	79–93%	Childhood	Review	Review
Ovary (ovaritis)	60%	2nd to 3rd decade	Endocrinology screen	Endocrinology screen
		3rd to 5th decade	Phosphocalcium levels	Phosphocalcium levels
		3rd decade	FSH, LH	FSH, LH
			E2	E2
			Or testosterone	Or testosterone
Testis	<25%			
Thyroiditis	3–10%		TSH, AC anti-TPO	TSH
Type 1 diabetes	2–12%	2nd to 3rd decade	Fasting blood glucose, AB anti-IA2, anti-insulin, anti-GAD	Fasting blood glucose
Lymphocytic hypophysitis	5–7%	Childhood	IGF1, FSH, LH, ACTH	IGF1, FSH, LH, ACTH
Gastroenterology manifestations			Examinations	Examinations, clinical examination
Malabsorption	15–18%	Childhood	Clinical examination	Serum albumin and ferritin
			Seum albumin and ferritin	
			AB anti-GAD65	
Hepatitis	12–20%	Childhood	Hepatic function markers	Hepatic function markers
			NFS, vitamin B12, anti-intrinsic factor and antigastric parietal cell antibodies	NFS, vitamin B12
Gastritis	13–15%	2nd to 3rd decade		
Gastroenterology manifestations			Examinations,	Examinations, clinical examination
Malabsorption	15–18%	Childhood	Clinical examination	Serum albumin and ferritin
Hepatitis	12–20%	Childhood	Seum albumin and ferritin	Hepatic function markers
Gastritis	13–15%	2nd to 3rd decade	AB anti-GAD65	NFS, vitamin B12
			Hepatic function markers	
			NFS, vitamin B12, anti-intrinsic factor and anti-gastric parietal cell antibodies	
Other non-endocrine manifestations				
Interstitial nephritis	<10%	2nd to 3rd decade	Urea, creatinine, TA, plasma ions	Urea, creatinine, TA, plasma ions
			Clinical examination + _ EFR and TDM if clinically indicated	Clinical examination + _ EFR and TDM if clinically indicated
HTA with hypokalemia	15%	Childhood or young adult	NFS, examination for Howell	NFS, examination for Howell
Obliterative bronchiolitis	10–20%		Jolly bodies	Jolly bodies
Splenic atrophy			Abdominal ultrasound	Clinical examination
Auto-immune hemolytic anemia, large granular lymphocytic leukemia			Clinical examination	
Severe infections				
Myocarditis				
Pulmonary hypertension				
Progressive muscular atrophy				
Vasculitis				
Connective tissue disease				
Febrile skin rashes				
Anxiety, depression				

R5-2: in adults with an adrenal crisis, we recommend administration of one liter of isotonic saline in the first hour. The speed of infusion and the volume of isotonic saline (with 10% glucose in cases of hypoglycemia) administered should be modified according to clinical and hemodynamic monitoring of the patient. Treatment should be maintained for 24–48 h. In ACTH insufficiency, treatment should also include isotonic saline IV infusion to correct fluid and electrolyte loss, especially in cases of digestive problems and/or hypotension.

Strong recommendation. Expert opinion.

R5-3: in prepubertal children with an adrenal crisis, we recommend:

- administration of injectable hydrocortisone hemisuccinate (100 mg ampoule) 2 mg/kg/6 h in IV drip or each 6–8 h via IM or SC injection;
- parenteral rehydration using 5% glucose or 10% glucose in cases of hypoglycemia with provision of NaCl of 10–15 mEq/kg/day (maximum 408 mEq/day = 24 g, plasma sodium must not increase by more than 1 mEq/kg/hr) and provision of fluids according to the age of the patient: newborn: 150–180 mL/kg/day; child: 2.5–3 L/m²/day. Volume replacement with isotonic saline in case of circulatory collapse (10–20 mL/kg) is sometimes necessary;
- clinical monitoring (blood pressure, heart rate, glycemia, urine output, weight, alertness) and biochemical monitoring, adapted for fluid and electrolytes and the speed of their correction, is essential.

Strong recommendation. Expert opinion.

drome type 1, see [Table 4](#); illnesses with underlying monogenic causes). The transition period between adolescence and adulthood represents an added risk of a breakdown in monitoring which requires particular attention from medical teams and coordination between adult and pediatric medical teams.

It is essential to encourage patient autonomy in the management of their illness, notably their participation in treatment education programs, especially programs that target avoidance of, or early treatment of acute adrenal insufficiency. The principal educational objectives for patients in such programs are:

- to be in possession of, and carry the necessary tools for their treatment in an emergency;

R5-4: in adults we suggest on the day of surgery or intervention, an IM or IV injection of a 100 mg bolus of hydrocortisone hemisuccinate, followed in the case of major surgery, by continuous infusion of hydrocortisone hemisuccinate, 100 mg/24 h (or alternatively 25 mg IM or IV every 6 h), to be continued until patients return to eating. On return to oral treatment, normal dose should be tripled (at least 60 mg/day), taken three times per day (morning, midday and evening) before gradual reduction of the dose over a few days to the normal dose. In primary adrenal insufficiency, treatment with fludrocortisone should be recommended when the hydrocortisone dose has been reduced to <50 mg/day.

Weak recommendation. Expert opinion.

R5-5: in children, we suggest that on the day of the intervention the same protocol as that used in cases of acute adrenal insufficiency be employed, and continued until the patient returns to eating. When oral treatment is recommended, the normal dose of hydrocortisone should be tripled and taken in three administrations per day (morning, midday and evening) before progressively reducing the dose over several days to the normal dose. In cases of light anesthesia, minor surgery or examination that requires fasting conditions, we suggest hydrocortisone hemisuccinate 2 mg/kg/4–6 h by IV injection or each 6–8 h by IM injection, to be continued if the fasting state continues, and after to return to normal oral hydrocortisone administration.

Weak recommendation. Expert opinion.

- to be able to identify situations of increased risk and the early signs of adrenal crisis;
- to know how to adjust their oral glucocorticoid treatment;
- to be capable of administering hydrocortisone by subcutaneous injection;
- to be able to predict and therefore adjust treatment to different situations (heat, physical exercise, travel);
- to be able to correctly use the appropriate resources of the healthcare services.

Other programs could also be developed to respond to needs and expectations of patients, notably concerning the adjustment of hydrocortisone dosage to avoid overdose in the context of chronic fatigue syndrome.

R5-6: in childbirth, we suggest the administration to the mother of hydrocortisone hemisuccinate by infusion (syringe pump) 100 mg/24 h (alternatively 25 mg by IM or IV injection each 6 h) during the period of labor.

After delivery and in the absence of complications, oral administration can be recommenced using triple the normal dose, taken in three doses across the day before a progressive reduction of the dose and gradual return to normal dosing.

In the case of caesarean section: recommendations are the same as for major surgery. We suggest IM or IV injection of a bolus of 100 mg hydrocortisone hemisuccinate followed by continuous infusion of 100 mg/24 h (or alternatively 25 mg by IM or IV injection every 6 h) until the patient returns to oral intake of food. Oral administration of hydrocortisone is then recommenced with triple the normal dose, taken as three doses during the day and then a progressive reduction to return to normal dosing.

Written recommendations for the peri- and post-partum period should be provided to the pregnant patient, obstetricians and anesthetists ensuring that they are followed.

Weak recommendation. Expert opinion.

R5-7: in the adult patient, we suggest that colonoscopy procedures be programmed in the morning. We suggest that a supplementary dose of 20 mg hydrocortisone is taken the evening before and on the morning of the examination, combined with normal oral hydration. Immediately prior to the procedure, an IM or IV injection of 100 mg hydrocortisone hemisuccinate should be administered. From the next day the patient can recommence oral hydrocortisone at the normal dose.

In case of clinical signs suggesting adrenal crisis during the preparation for the examination (intense fatigue, nausea, hypotension) an IM or SC injection of 100 mg hydrocortisone hemisuccinate is recommended.

Strong recommendation. Expert opinion.

R5-8: in the adult patient, we recommend, when presenting with acute intercurrent illness, the administration of hydrocortisone hemisuccinate 100 mg/24 h by continuous IV infusion by syringe pump (or alternatively 25 mg by IM or IV injection every 6 h).

After correction of the clinical condition and of hemodynamic parameters, we recommend recommencing oral hydrocortisone at triple the normal dose (at least 60 mg/24 h) administered in three doses per day and with a progressive reduction over several days to return to the normal dose. In patients with primary adrenal insufficiency, treatment with fludrocortisone can be recommenced when the hydrocortisone dose is less than 50 mg/day.

Strong recommendation. Expert opinion.

R5-9: in the pediatric patient, in case of acute intercurrent illness requiring administration of parenteral hydrocortisone hemisuccinate, we recommend a dose of 1–2 mg/6 h by IV drip or each 6–8 h by IM injection, depending on the clinical state. After correction of the clinical state and hemodynamic parameters, we recommend recommencing oral hydrocortisone treatment with triple the normal dose, taken in 3 administrations per day and with a progressive decrease in dose over several days to return to normal doses. Fludrocortisone can be reintroduced at the same time as oral hydrocortisone is recommenced.

Strong recommendation. Expert opinion.

nents, one that is rapidly released and the other resulting in prolonged release over 12 hours. It does not, however, mimic the peak of cortisol secretion on waking. Duocort treatment during a 6-month period was associated with favourable changes in weight, blood pressure and glycemic control in patients with diabetes mellitus, in comparison with hydrocortisone.

Another modified release hydrocortisone (Chronocort[®]) is currently being evaluated for the indication “adrenal enzymatic block”. One administration in the evening at 10 pm results in a physiological increase in cortisol during the night. There is therefore the potential for producing, with this drug, a physiological increase in nocturnal concentration of hydrocortisone. The drug is effective in controlling androgen excess in adults with congenital adrenal hyperplasia. Recently, the new multiparticulate formulation Infacort was designed for the treatment of adrenal insufficiency during infancy. These new compounds may help obtaining a physiological glucocorticoid replacement with potential short term and long-term beneficial consequences on

2.7. Perspectives [4]

The modified release hydrocortisone Duocort (Plenadren[®]) has recently been authorized for use in Europe for patients with adrenal insufficiency. This formulation gives a release profile that is more physiological across the day, with two compo-

R5-10: we recommend:

- that all patients are given a card identifying them as requiring urgent medical care, marked "adrenal insufficiency";
- that patients and parents of pediatric patients be educated as to the risks of adrenal insufficiency, how to increase the dose of hydrocortisone themselves in cases of stress, infection, trauma and how to adapt their treatment to altered circumstances (heat, physical exercise, travel);
- patients and their family/carers should be educated in how to perform SC injections of hydrocortisone hemisuccinate;
- all patients should be provided with prescriptions for 100 mg vials of hydrocortisone hemisuccinate, syringes and needles for preparation and delivery of the injection. Patients always need to carry the necessary materials for injection with them;
- there should be regular evaluation of patient knowledge, as well as that of their family/carers and their physician, about their condition.

Strong recommendations. Expert opinion.

R6.1: we recommend that adults with adrenal insufficiency have regular consultation by an endocrinologist at least once per year.

Strong recommendations. Expert opinion.

R6.2: we recommend that children with adrenal insufficiency have regular consultation by a pediatric endocrinologist in a specialised center or reference center two to three times per year and more frequently in babies.

Strong recommendations. Expert opinion.

quality of life, morbidity and mortality in the adrenal insufficient patient.

Disclosure of interest

F. Castinetti has performed conferences for HAC Pharma, Shire and Viropharma. L. Guignat was a consultant for Viropharma and has performed conferences for HAC Pharma. C. Bouvattier has been occasionally paid for conferences or writing for Sandoz and Ipsen laboratories. Y. Reznik was a consultant for Viropharma, and Shire and has performed conferences for HAC Pharma and Viropharma. O. Chabre has performed confer-

R6-3: in adults, we suggest clinical monitoring based on evidence of signs of over- or under-dosage, particularly for preventing the consequences of chronic overdose in bone, metabolic and cardiovascular parameters. For adjustment of glucocorticoid replacement, we do not recommend routine use of hormonal markers.

In children, we recommend clinical monitoring (growth, puberty) and examination for clinical signs of overdose or under-dosage. We do not recommend routine use of biochemical markers for adjustment of replacement therapy until further validation, except in congenital adrenal hyperplasia where we recommend regular assay of specific biochemical markers. In cases other than congenital adrenal hyperplasia, assay for ACTH is sometimes useful for evaluation of treatment compliance.

In adults and children, for adjustment of mineralocorticoid replacement, we suggest clinical monitoring (blood pressure, salt appetite, lower limb edema) and examination for biochemical signs of under-dosing (hyponatremia, hyperkalemia, elevated renin) or overdosing (hypokalemia, undetectable renin levels or levels in the lower end of normal range).

Weak recommendation. Expert opinion.

R6.4: we recommend that patients with autoimmune primary adrenal insufficiency are examined systematically for associated auto-immune disorders, at least annually and more frequently in cases where there are early clinical signs of such disorders. The range of initial biochemical tests (excluding auto-immune polyendocrinopathy type I) includes: TSH, anti-thyroperoxidase antibodies; fasting blood glucose, anti-GAD antibodies, anti-IA2 (islet antigen 2) antibodies; blood cell count, vitamin B12, anti-gastric parietal cell antibodies, anti-intrinsic factor antibodies and anti-transglutaminase antibodies. The list of tests to be carried out in follow-up includes: TSH, fasted blood glucose, blood cell counts and vitamin B12. Women of child-bearing age should be warned of the risk of premature ovarian insufficiency. First-degree relatives should be warned of the signs of primary adrenal insufficiency and dys-thyroidism. We recommend regular screening for

ence for HAC Pharma. All other authors declare that they have no competing interest.

potential associated pathologies in the case of auto-immune polyendocrinopathy type 1 (Table 1) or in some genetic-linked adrenal insufficiencies.
Strong recommendation. Expert opinion.

R 6.5: we recommend a genetic counselling consultation in patients with adrenal insufficiency where an underlying genetic cause is suspected.
Strong recommendation. Expert opinion.

R 6.6: we recommend the development of patient education programs, particularly programs that aim to avoid or lead to early treatment of acute adrenal insufficiency, for the patients and their family or carers. We recommend the implementation of programs following the HAS (French national health authority) procedure including the stages of education in diagnosis, the application of the program and its evaluation. We recommend the inclusion of the following main educational objectives:

- to always carry the necessary emergency equipment;
- to be able to identify the situations at increased risk and the early symptoms of acute adrenal insufficiency;
- to know how to adjust oral glucocorticoids in acute situations or in anticipation of altered requirements, particularly in situations of: heat, physical exercise, travel, physical or psychological stress;
- to know how to administer hydrocortisone by subcutaneous injection;
- to appropriately use the resources of the health-care system;
- to be able to explain their pathology and its treatment to a member of their family or carer.

Strong recommendation. Expert opinion.

R6-7: we suggest that the dose of hydrocortisone be adjusted in situations likely to cause acute adrenal insufficiency (see Chapter 5), with

in adults, the dose of fludrocortisone being increased by 50 µg per 24 h in the case of extreme heat:

- for adult patients who usually take one 10 mg hydrocortisone tablet in the morning and one at midday, in situations likely to cause acute adrenal insufficiency, we suggest the following advice: “immediately take 2 tablets of hydrocortisone, regardless of the time of day, then 2 tablets in the morning, 2 tablets at midday and 2 tablets in the evening for 2–3 days until symptoms have gone”;
- for pediatric patients, we suggest to double or triple the dose of hydrocortisone, splitted into three doses per day, with one dose around midday and one at night. This regimen should be started immediately in the case of a situation of increased risk and continued until 24 h after symptoms have disappeared. We suggest that situations of prolonged fasting are avoided due to the risk of hypoglycemia.

Weak recommendation. Expert opinion.

R6-8: we suggest that an injection of hydrocortisone be delivered:

- after the second episode of vomiting or diarrhea in less than half a day;
- in the case of altered consciousness where oral administration is not possible;
- during childbirth, general anesthesia or in resuscitation/intensive care.

Weak recommendation. Expert opinion

R6-9: we suggest the following advice for particular circumstances: for intense and prolonged sporting activity in adults and adolescents: “take supplementary 5 mg hydrocortisone every 3 h, commencing 1 h before the start of physical activity”.

In case of air travel greater than 6hr in adults: “take supplementary 10 mg hydrocortisone every

6 h until breakfast time in the country where you arrive”.

In the case of extreme heat and/or excessive sweating: “drink more water than usual and add more salt to food; otherwise in adults, increase fludrocortisone by 50 mg”.

Weak recommendation. Expert opinion

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