

Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency

■ E. S. Husebye^{1,2}, B. Allolio³, W. Arlt⁴, K. Badenhoop⁵, S. Bensing⁶, C. Betterle⁷, A. Falorni⁸, E. H. Gan⁹, A.-L. Hulting⁶, A. Kasperlik-Zaluska¹⁰, O. Kämpe¹¹, K. Løvås^{1,2}, G. Meyer⁵ & S. H. Pearce⁹

From the ¹Department of Clinical Science, University of Bergen, Bergen, Norway; ²Department of Medicine, Haukeland University Hospital, Bergen, Norway; ³Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital Würzburg, Würzburg, Germany; ⁴Centre for Endocrinology, Diabetes and Metabolism, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; ⁵Department of Medicine 1, Goethe-University Hospital, Frankfurt am Main, Germany; ⁶Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden; ⁷Endocrine Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy; ⁸Department of Internal Medicine, Section of Internal Medicine and Endocrine and Metabolic Sciences, University of Perugia, Perugia, Italy; ⁹Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; ¹⁰Department of Endocrinology, Medical Center of Postgraduate Education, Warsaw, Poland; and ¹¹Department of Clinical Sciences, Uppsala University, Uppsala, Sweden

Abstract. Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting A-L, Kasperlik-Zaluska A, Kämpe O, Løvås K, Meyer G, Pearce SH (Department of Clinical Science, University of Bergen; Department of Medicine, Haukeland University Hospital, Bergen, Norway; Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital Würzburg, Würzburg, Germany; Centre for Endocrinology, Diabetes, and Metabolism, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; Department of Medicine 1, Goethe-University Hospital, Frankfurt am Main, Germany; Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden; Endocrine Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy; Department of Internal Medicine, Section of Internal Medicine and Endocrine and Metabolic Sciences, University of Perugia, Perugia, Italy; Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; Department of Endocrinology, Medical Center of Postgraduate Education, Warsaw, Poland; and Department of Clinical Sciences, Uppsala University, Uppsala, Sweden). Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. (Review). *J Intern Med* 2014; **275**: 104–115.

Primary adrenal insufficiency (PAI), or Addison's disease, is a rare, potentially deadly, but treatable disease. Most cases of PAI are caused by autoimmune destruction of the adrenal cortex. Consequently, patients with PAI are at higher risk of

developing other autoimmune diseases. The diagnosis of PAI is often delayed by many months, and most patients present with symptoms of acute adrenal insufficiency. Because PAI is rare, even medical specialists in this therapeutic area rarely manage more than a few patients. Currently, the procedures for diagnosis, treatment and follow-up of this rare disease vary greatly within Europe. The common autoimmune form of PAI is characterized by the presence of 21-hydroxylase autoantibodies; other causes should be sought if no autoantibodies are detected. Acute adrenal crisis is a life-threatening condition that requires immediate treatment. Standard replacement therapy consists of multiple daily doses of hydrocortisone or cortisone acetate combined with fludrocortisone. Annual follow-up by an endocrinologist is recommended with the focus on optimization of replacement therapy and detection of new autoimmune diseases. Patient education to enable self-adjustment of dosages of replacement therapy and crisis prevention is particularly important in this disease. The authors of this document have collaborated within an EU project (Euadrenal) to study the pathogenesis, describe the natural course and improve the treatment for Addison's disease. Based on a synthesis of this research, the available literature, and the views and experiences of the consortium's investigators and key experts, we now attempt to provide a European Expert Consensus Statement for diagnosis, treatment and follow-up.

Keywords: 21-hydroxylase, Addison's disease, adrenal crisis, autoimmune polyendocrine syndrome, cortisol.

Introduction

Patients with primary adrenal insufficiency (PAI), which is also called Addison's disease, present with symptoms that result from the lack of the glucocorticoid and mineralocorticoid hormones that are normally produced in the adrenal cortex, irrespective of the aetiology of the condition. The predominant cause of PAI in Europe is autoimmunity [1]. Approximately one-half of the patients with PAI have other co-existing autoimmune diseases [1–5], such as autoimmune thyroid disease, autoimmune gastritis with vitamin B12 deficiency and type-1 diabetes mellitus [1–4]. Premature ovarian insufficiency (POI) [1, 5, 6], vitiligo and coeliac disease [7–9] are also common. These combinations are classified into several polyendocrine syndromes [10]. Autoimmune polyendocrine syndrome type-1 (APS-1) is caused by mutations in the *autoimmune regulator (AIRE) gene* and is defined as the combination of two of the following three components: PAI, hypoparathyroidism and chronic mucocutaneous candidiasis [11, 12]. Autoimmune polyendocrine syndrome type-2 (APS-2) denotes the cluster of organ-specific autoimmune diseases with a complex pattern of inheritance [13] and most commonly involves PAI with primary hypothyroidism. A spectrum of other conditions, including hyperthyroidism due to Graves' disease, autoimmune gastritis with vitamin B12 deficiency and type 1 diabetes, are also encountered.

Why are recommendations needed?

Prior to the 1940s, PAI was always fatal. The synthesis of corticosteroids by Kendall and Reichstein made life-saving treatments possible and transformed Addison's disease into a fully treatable chronic condition. Unfortunately, premature death from adrenal crises is still a problem, and patients are at risk of therapy-related osteoporosis and cardiovascular complications [14, 15]. The quality of life and ability to work is reduced in many patients, and there are concerns about fertility in women due to an increased risk of autoimmune POI [5] and sexual dysfunction due to the lack of androgens [16]. These issues are addressed in an accompanying review. PAI is a rare disease and has a prevalence of 10–15 per 100 000 population. Most physicians, and even specialists in endocrinology, rarely manage more than a few patients with PAI. The procedures for diagnosis of PAI, treatment for the disease and follow-up vary greatly within Europe. The aims of the 7th framework

programme project of the EU, Euradrenal (www.euradrenal.org), were to study the pathogenesis, describe the natural course and improve the treatment for Addison's disease [1]. Based on a synthesis of the Euradrenal research, the views and experience of the consortium investigators, and the available literature, we now attempt to provide a European Expert Consensus Statement for diagnosis, treatment and follow-up (Table 1).

Recommendations on diagnosis of primary adrenal insufficiency

The diagnosis of PAI requires two steps. First, the function of the adrenal cortex should be assessed. Once PAI is confirmed, it is mandatory to establish the aetiology (Fig. 1). The laboratory finding of hyponatraemia is present in 90% of newly presenting cases, but the classical combination of hyponatraemia and hyperkalaemia are not reliable markers for making a diagnosis because the serum levels of sodium are often only marginally reduced, whilst the serum levels of potassium are only increased in approximately one-half of the patients at the time of diagnosis. Hyponatraemia is caused by the loss of sodium in urine and increases in both plasma vasopressin and angiotensin II, which impair free water clearance. Hyperkalaemia is caused by aldosterone deficiency, impaired glomerular filtration and acidosis. Importantly, in the presence of severe vomiting, hypokalaemia and alkalosis may be present. Between 10% and 20% of patients have mild or moderate hypercalcaemia at presentation. Anaemia, mild eosinophilia, lymphocytosis and increased liver transaminases [17] may also be present. Children, but rarely adult patients, are prone to hypoglycaemia, and even hypoglycaemic seizures may occur.

At the time of diagnosis, serum cortisol is usually below the normal range, and the plasma ACTH level is clearly increased; however, in some patients presenting with serum cortisol levels within the normal range, the level is inappropriately low for the disease state, such as patients with sepsis [18]. Exogenous steroid use (oral prednisolone or dexamethasone) and inhaled steroids (fluticasone) may confound interpretation of low serum cortisol levels. The plasma renin activity (PRA) is increased, whilst the serum aldosterone and dehydroepiandrosterone sulphate (DHEAS) levels are low [16]. Patients who present with PAI can have TSH levels that are increased, usually in the range of 4–10 IU L⁻¹, because of the lack of the inhibitory effect of cortisol on TSH production [19]. Alterna-

Table 1 Summary of recommendations

Area	No	Recommendation*
Diagnosis	1	The diagnosis of PAI should be considered in all patients presenting with unexplained collapse, hypotension, vomiting or diarrhoea. Hyperpigmentation, hyponatraemia, hyperkalaemia, acidosis and hypoglycaemia increase clinical suspicion of PAI
	2	Treatment of suspected acute adrenal insufficiency should never be delayed by diagnostic procedures
	3	The diagnostic test for primary PAI should be paired measurement of serum cortisol and plasma ACTH. In equivocal cases, a synacthen (tetracosactide) stimulated (0.25 mg im or iv) peak serum cortisol <500 nmol L ⁻¹ is diagnostic of PAI
	4	S-cortisol <250 nmol L ⁻¹ and increased ACTH in the presence of acute illness (suspected acute adrenal insufficiency) is diagnostic of primary PAI. S-cortisol <400 nmol L ⁻¹ and increased ACTH in the presence of acute illness raises a strong suspicion of PAI
Aetiology	5	The aetiology of PAI should be ascertained starting with the measurement of serum 21-hydroxylase (anti-adrenal) autoantibodies
	6	If antibodies are negative, CT imaging is recommended. In male patients, assay very long-chain fatty acids to check for adrenoleukodystrophy
	7	The diagnosis of APS-1 should be considered in children and young persons presenting with PAI and other diagnostic clinical manifestations (e.g. hypoparathyroidism and candidiasis). APS-1 diagnosis can be confirmed by the presence of anti-interferon omega antibodies, or mutational analysis of the <i>AIRE</i> gene
Therapy	8	All patients with adrenal insufficiency should wear Medic Alert identification jewellery and carry a steroid/alert card. They should receive sufficient education to manage daily medications and situations of minor to moderate concurrent illnesses. Supplies to allow self-injection of parenteral HC should be provided
	9	Most patients with primary adrenal insufficiency should take 15–25 mg of HC (18.75–31.25 mg of CA) daily in split doses; first dose immediately after waking, and the last dose not <6 h before bedtime. HC in children should be 6–10 mg m ⁻² of body surface area. The lowest dose compatible with health and a sense of well-being should be used
	10	Most patients with PAI should take 50–200 µg fludrocortisone as a single daily dose. Children and younger adults may require higher doses. If essential hypertension develops, the dose of fludrocortisone should be reduced, but not stopped. Patients should be advised to take salt and salty foods <i>ad libitum</i> and avoid liquorice and grapefruit juice
	11	There is insufficient evidence of benefit to recommend routine replacement of adrenal androgens
	12	Surgery and invasive medical procedures often require iv or im HC and increased oral doses. Small adjustments to HC and fludrocortisone doses may be needed during pregnancy, particularly during the last trimester; parenteral doses of hydrocortisone should be given during delivery
	13	Adrenal crisis should be treated immediately with iv or im HC, 100 mg followed by 100 mg 6–8 hourly until recovered. Isotonic (0.9%) sodium chloride solution should usually be administered, at an initial rate of 1 L h ⁻¹ until haemodynamic improvement. The underlying precipitant of adrenal crisis (e.g. infection) should be sought, once treatment has been initiated
Follow-up	14	Patients with PAI should be reviewed at least annually, with assessment of health and well-being, measurement of weight, blood pressure and serum electrolytes. Occasional monitoring for the development of new autoimmune disorders, particularly hypothyroidism, is worthwhile. Assessment for the complications of glucocorticoid therapy should include monitoring of bone mineral density every 3–5 years

PAI, primary adrenal insufficiency; HC, hydrocortisone; CA, cortisone acetate.

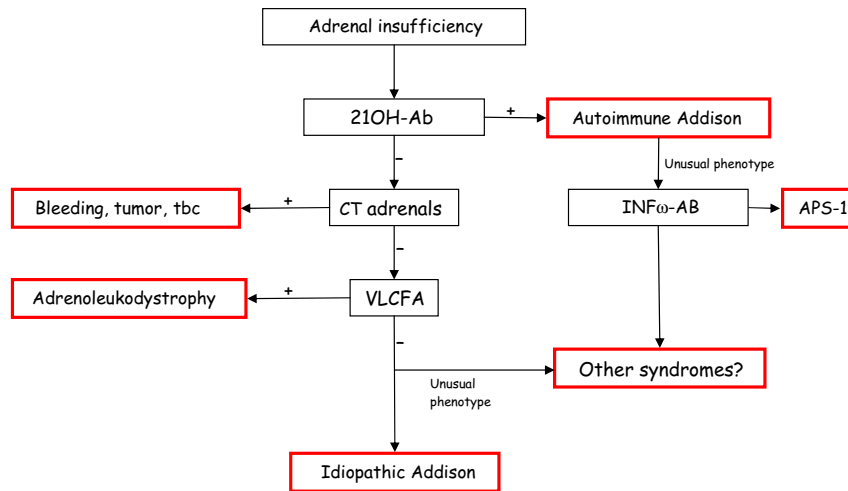


Fig. 1 Algorithm for diagnostic workup of Addison's disease.

tively, increased TSH is caused by a concomitant autoimmune hypothyroidism accompanied by autoantibodies against thyroperoxidase (TPO-Ab).

When uncertainty exists whether or not partial PAI is present, a cosyntropin (synacthen or tetracosactide) test may be necessary. The standard test requires administration of 0.25 mg cosyntropin intramuscularly or intravenously, followed by measurement of serum cortisol after 30 and/or 60 min. One of these values should exceed 500 or 550 nmol L⁻¹ to be deemed normal. Synacthen tests are also useful in patients at risk of developing PAI, such as individuals with 21-hydroxylase autoantibodies (21OH-Ab) without overt PAI, and patients with APS-1 without PAI.

It should be emphasised that if there is a clinical suspicion of impending acute adrenal crisis, the patient should be given intravenous hydrocortisone (HC) immediately and a physiologic (0.9%) saline infusion. Treatment should never be delayed because of the need to carry out diagnostic procedures, but blood samples for cortisol and ACTH measurement should be secured prior to treatment if possible. The diagnosis can always be established later, even if treatment has commenced.

Aetiologic diagnosis

Once the diagnosis of PAI has been confirmed, the aetiology should be determined because the aetiology may affect treatment decisions and follow-up. In Western Europe, autoimmunity accounts for

approximately 85% of diagnoses of PAI after congenital adrenal hyperplasia has been excluded. The diagnosis of an autoimmune cause is based on measurements of circulating 21OH-Ab [20]. Other causes of PAI are due to a number of causes, including tuberculosis, adrenal haemorrhage and genetic disorders (Table 2).

To establish an aetiological diagnosis, the first test is to assay 21OH-Ab, preferably by a validated method. A commercial kit is available from FIRS Laboratories (RSR, Cardiff, UK), but some research laboratories also perform the test. A proficiency study comparing various assays of 21OH-Ab showed that nearly all laboratories offering such a test have broadly comparable results. If the test is positive, further aetiological evaluation is not generally necessary. The rare disease, APS-1, should be considered in young patients if one or more of the other components of APS-1 are present, such as hypoparathyroidism, candidiasis, dental enamel dysplasia, keratitis, autoimmune hepatitis, malabsorption or POI [12]. In these cases, evaluation should be extended to include measurement of interferon omega or IL-22 autoantibodies [21–23], and if possible, a mutational analysis of *AIRE* gene. Rare 21OH-Ab-positive cases have recently been reported as part of the mitochondrial disorder, Kearns–Sayre syndrome [24].

In patients without 21OH-Ab, which may represent a nonautoimmune form of Addison's disease, a more thorough investigation must be undertaken [25]. 21OH-Ab are often absent in children and the elderly

Table 2 Classification and causes of primary adrenal insufficiency

Aetiology	Pathogenesis	Diagnosis
Autoimmune	T and B cell autoimmunity against adrenocortical cells	21OH-Ab
Infection	Mycobacteria Bacteria (e.g. meningococcus and Haemophilus influenzae) Fungus (e.g. <i>Pneumocystis carinii</i>) Virus (e.g. HIV, herpes simplex and cytomegalovirus)	Culture, Quantiferon test, PCR, adrenal CT
Bleeding	Antiphospholipid syndrome Anticoagulant therapy Disseminated intravascular coagulation	Evidence of bleeding on adrenal CT
Surgery	Tumour surgery, Cushing's syndrome, Radical nephrectomy	
Genetic	Congenital adrenal hyperplasia Adrenoleukodystrophy Hypogonadotropic hypogonadism, Familiar glucocorticoid deficiency (ACTH resistance syndrome), Smith-Lemli-Opitz syndrome, mitochondrial forms (Kearns-Sayre syndrome)	Urine steroid profile, sequencing of steroidogenic genes (e.g. <i>CYP21B</i>) Measure VLCFA Sequencing of <i>NROB1 (DAX1)</i>
Infiltrative	Amyloidosis, haemochromatosis, bilateral adrenal metastasis or lymphoma, xanthogranulomatosis	
Medication	Ketoconazole, etidomate, mitotane, metyrapone	

– in the former often due to genetic causes [26], and in the latter due to tuberculosis, haemorrhage, malignant disorders and drugs (for an extended list of causes, see Table 2). In investigating such patients, a computer tomography scan of the adrenal glands should be performed as a first means to demonstrate tumours or the calcifications typical of tuberculosis. Males should be screened for adrenoleukodystrophy, an X-linked condition with wide variation in clinical presentation, by measuring very long-chain fatty acids in a serum sample. A different X-linked condition with PAI associated with delayed or incomplete puberty due to hypogonadotropic hypogonadism is caused by mutations in the *NROB1 (DAX1)* gene [27]. Other investigations must be guided by history and physical examination of the patient (Fig. 1). It should be kept in mind that with time, previously 21OH-Ab-positive patients may become negative. Thus, a lack of 21OH-Ab does not exclude autoimmunity.

Guidelines on chronic replacement therapy

General principles

Patients with PAI require lifelong steroid replacement, both glucocorticoids and

mineralocorticoids, and often an increased intake of sodium chloride to compensate for increased renal loss. Education on how to increase steroid doses during concurrent illnesses or injury is important, as well as training in intramuscular administration of HC during acute adrenal crisis (*vide infra*). Patients should wear a Medic Alert Bracelet and carry a steroid card to inform medical personnel on chronic PAI status (Fig. 2). Delays in the administration of HC in an emergency or stress situation by the patient or healthcare professionals can be fatal. The sad fact remains that many patients have to argue with the attending physician or emergency department staff to receive emergency treatment, and this must be overcome by improved information.

Glucocorticoid replacement

Glucocorticoids are secreted into the systemic circulation in a pulsatile (ultradian) and circadian fashion, with a peak in the morning and reaching a nadir at midnight. Individuals with normal adrenal function produce between 5 and 10 mg of cortisol per m² of body surface area per day [28], equivalent to an oral replacement dose of 15–25 mg day⁻¹ of HC.

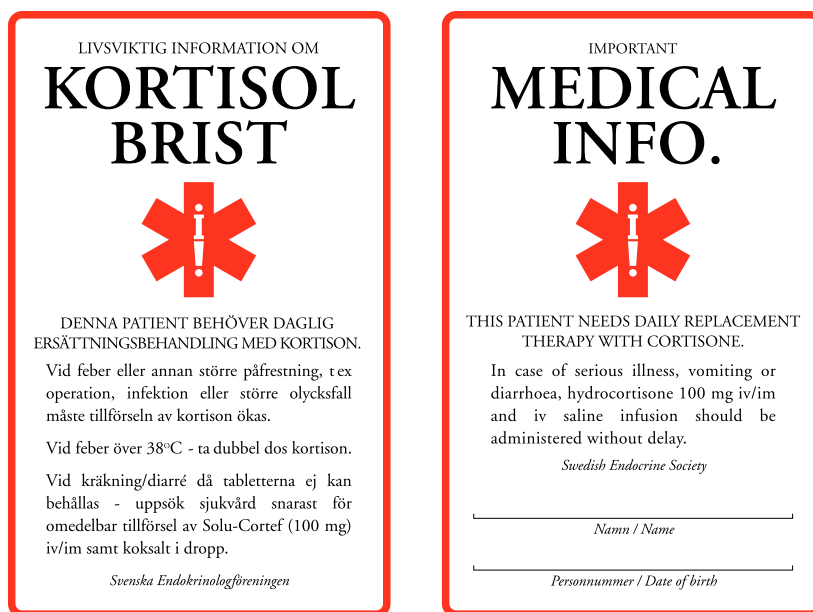


Fig. 2 The Swedish duplex steroid card for adults with English and Swedish text. A version for children also exists. Equivalent cards are also used in Norway.

The preferred choice of glucocorticoid treatment is HC or cortisone acetate (CA); no studies have shown that one is superior to the other. CA has a slightly delayed onset of action as it needs to be activated to HC by hepatic 11 β -hydroxysteroid dehydrogenase (HSD) type 1. HC is available in 20, 10 and 2.5 mg tablets, whilst CA is available in 25 and 5 mg tablets. Both HC and CA are taken in two or three divided doses, with the first dose upon awakening and the last dose approximately 4–6 h before bedtime. Only relatively small studies have compared dosing regimens [29, 30]. Standard dose regimens are given in Table 3.

CYP3A4 is the key drug metabolizing enzyme affecting HC clearance and concomitant administration of several drugs can affect HC efficacy, as shown in Table 4. Plasma ACTH and serum cortisol are not useful parameters for glucocorticoid dose adjustment. Therefore, monitoring of glucocorticoid replacement predominantly relies on clinical assessment. Symptoms and signs of over-replacement are weight gain, insomnia and peripheral oedema, whilst under-replacement is characterized by lethargy, nausea, poor appetite, weight loss and increased pigmentation that often has an uneven distribution. In addition to patient weight, fine-tuning of the daily HC dosage may be achieved by detailed questioning about the daily

intake of tablets, general feelings of energy and 'get up and go', mental concentration, daytime somnolence and changes in pigmentation. Information about low points or dips in energy during the day and knowledge of the time a patient goes to bed and ease in getting to sleep can also prove invaluable. In cases in which malabsorption is suspected, serum or salivary cortisol day curve monitoring may be useful to guide dosing. In this situation, a morning, postdose peak level and trough predose levels for subsequent dosages are the most useful in adjusting dose timings and quantities.

Dosing in different situations

Lack of appetite or nausea and vomiting in the morning are common symptoms in PAI patients. Waking up earlier to take the first dose of HC and then going back to sleep may relieve these symptoms. Patients who work night-time shifts will need to adjust their dose schedule according to the work pattern (e.g. 10 mg upon awakening before going to work, instead of taking the first dose at 07:00 h). Dexamethasone should be avoided, but prednisolone may have a role in a few select patients who experience marked fluctuations in energy or well-being over the course of the day. Typical prednisolone doses are 4 or 5 mg on awakening, or 3 mg on awakening and 1 or 2 mg at 14:00 h.

Table 3 Glucocorticoid replacement in primary adrenal insufficiency

Glucocorticoid	Dose range (mg day ⁻¹)	Typical dose regimen (mg)	Long-shift regimen (mg) ^a
Hydrocortisone	15–25	Three doses (07:00, 12:00, 16:00 ± 1 h) 15 + 5 + 5; 10 + 5 + 5; 10 + 5 + 2.5; 7.5 + 5 + 2.5	10 + 5 + 2.5 + 2.5..... + 2.5
		Two doses (07:00, 12:00 ± 1 h) 15 + 5; 10 + 10; 10 + 5	
Cortisone acetate	25–37.5	Three doses (07:00, 12:00, 16:00 ± 1 h) 12.5 + 12.5 + 12.5; 12.5 + 12.5 + 6.25; 12.5 + 6.25 + 6.25	12.5 + 6.25 + 6.25 + 6.25 + 6.25
		Two doses (07:00, 12:00 ± 1 h) 25 + 12	
Prednisolone ^b	4–5	One dose (07:00) 4 or 5 mg	Prednisolone
		Two doses (07:00, 14:00 ± 1 h) 3 + 2; 3 + 1	

^aAirline stewardess, postman.

^bShould only be considered if the event of compliance problems, marked fluctuations of energy and when HC/CA is not tolerated.

Table 4 Medications and food interacting with hydrocortisone and cortisone acetate

Drugs that affect hydrocortisone metabolism	Hydrocortisone/cortisone acetate dose changes
Anti-epilepsy/ barbiturates	May need more
Antituberculosis	May need more
Antifungal drugs	May need to be changed
Etomidate	May need more
Topiramate	May need more
Grapefruit juice	May need less
Liquorice	May need less

A modified release hydrocortisone formulation (Plenadren) allowing once daily dosing, has recently been introduced in Europe, but its role in therapy is currently being evaluated.

Mineralocorticoid replacement

Mineralocorticoids are vital for maintaining blood pressure, and water and electrolyte homeostasis. The synthetic mineralocorticoid, 9 α -fludrocorti-

sone, is used as replacement therapy and is taken once daily in the morning. Patients are advised to eat sodium salt and salty foods without restriction and to avoid potassium-containing salts, which are often marketed as 'healthy'. To allow unrestricted sodium intake and avoid salt craving is an important third component of the substitution therapy. The amount of fludrocortisone required is related to individual fluid and electrolyte intake/losses. A daily dose of 50–200 μ g is usually sufficient in primary PAI, but a higher dose (up to 500 μ g daily) is sometimes needed in children and younger adults or in the last trimester of pregnancy when high levels of progesterone counteract mineralocorticoids [31].

The currently available forms of fludrocortisone preparation include 0.1- and 0.05-mg tablets. The tablets are usually taken in one dose upon awakening. The new formulation instructions (e.g. for FlorinefTM) require patients to keep the medication refrigerated. The actual decay rate is, however, only 0.1% in the first 6 months at room temperature. Mineralocorticoid replacement is evaluated clinically by asking the patient about salt cravings or lightheadedness, measuring blood pressure in the supine and standing positions, and identifying the presence of peripheral oedema. Fludrocortisone

Table 5 Medications that interact with fludrocortisone

Drugs that affect fludrocortisone	
Diuretics	Avoid
Acetazolamide	Avoid
Carbenoxolone, liquorice	Avoid
NSAIDs	Avoid
Drospirenone-containing contraceptive	May need more

under-replacement is common, and sometimes compensated for by over-replacement of glucocorticoids, and possibly predisposes patients to recurrent adrenal crises. Diuretics and drugs that affect blood pressure and electrolytes might interact with fludrocortisone and may require dose adjustments, as shown in Table 5. Liquorice and grapefruit juice potentiate the mineralocorticoid effect of HC and should be avoided [32].

Essential hypertension in a patient with PAI should be treated by adding a vasodilator, not by stopping the mineralocorticoid replacement, although a dose reduction should be considered.

Adrenal androgen replacement

Patients with PAI are deficient in adrenal androgen secretion, including dehydroepiandrosterone (DHEA), and this can result in severe androgen deficiency in female patients. In women with PAI, adrenal androgen can be replaced by oral DHEA tablets (10–50 mg), often 25 mg as a single daily dose guided by serum DHEA sulphate (DHEAS), androstenedione and testosterone levels, which should be maintained in the normal range when measured in the morning prior to DHEA ingestion; there is only limited objective evidence of clinical benefit from large studies [16, 33]. A pragmatic approach is to offer female patients with a persistent lack of libido and/or low energy levels despite optimized glucocorticoid and mineralocorticoid replacement a 6-month trial of DHEA replacement, which can be continued if clinically effective. Because the long-term effects of DHEA or testosterone replacement therapy in patients with PAI are not known, such a regimen should be used with caution.

Steroid replacement in pregnancy

Pregnancy is associated with a gradual, but pronounced physiologic increase in corticosteroid-

binding globulin (CBG) and total serum cortisol, following oestrogen-induced hepatic production of CBG. Free cortisol levels rise during the third trimester, resulting in an increased requirement for HC by 2.5 or 10 mg daily. Serum progesterone has anti-mineralocorticoid effects, and hence, the fludrocortisone dose may often need to be increased during late pregnancy [31]. PRA is not a good parameter for fludrocortisone dose adjustment in this scenario as the PRA levels normally increase during pregnancy, leaving evaluation of salt cravings, blood pressure and serum electrolytes as the best means for dosage monitoring. During delivery, a bolus parenteral dose of 100 mg of HC (Solu-CortefTM) should be given and repeated if necessary every 6 h. The oral dose should be doubled for 24–48 h postpartum (Table 6).

Steroid replacement during surgery and medical procedures

Patients with PAI need to increase steroid doses during surgery and medical procedures according to the degree of stress induced. We advise using the recommendations developed by the UK Addison's disease self-help group and the physicians of the Addison's disease clinical advisory panel (Table 6).

Steroid replacement during physical activity

PAI patients undergoing regular, accustomed and time-limited physical activity do not generally need to make a dose adjustment. In the face of unaccustomed, intense or prolonged exercise, however, an increase in HC and salt intake may be necessary. For running a race, such a marathon, an extra 5 mg of HC can be taken before the race. In hot conditions or during intense activity, additional fluid and salt intake should be taken to replace sweat losses. Patients planning to undertake such intense or prolonged exercise should be advised to test out their proposed replacement regimen before the event; however, there are no systematic studies of replacement therapy during strenuous physical activity.

Guidelines for treatment of an adrenal crisis

The nature and cause of an adrenal crisis

An acute adrenal crisis is a life-threatening emergency that requires immediate diagnosis and treatment. Even a mild upset stomach may be a precipitating event as patients do not absorb their medication when they need the medication more

Table 6 Treatment during surgery, dental procedures, delivery and invasive procedures^a

Procedure	Preoperative needs	Postoperative needs
Major surgery with long recovery time	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h until able to eat and drink. Then double oral dose for 48+ h, then taper to normal dose
Major surgery with rapid recovery	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h for 24–48 h. Then double oral dose for 24–48 h, then taper to normal dose
Labour and vaginal birth	100 mg hydrocortisone im just at onset of labour	Double oral dose for 24–48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery	100 mg hydrocortisone i/m just before anaesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives	Hospital admission overnight with 100 mg hydrocortisone im and fluid, repeat dose before start of procedure	Double oral dose for 24 h, then return to normal dose
Other invasive procedures	100 mg hydrocortisone im just before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental procedure	Extra morning dose 1 h prior to surgery	Double oral dose for 24 h, then return to normal dose
Minor procedure	Usually not required	Extra dose (e.g. 20 mg hydrocortisone) if symptoms

^aMaterial reproduced from UK Addison's disease self-help group; www.addisons.org.uk.

than ever. Prompt recognition and therapy is vital for the patient, but unfortunately this is not always the case. The frequency of acute adrenal crises among patients with PAI is 6–8 per 100 patient-years, and precipitating events are often vomiting and/or diarrhoea, infections, surgical procedures, injuries, myocardial infarction, severe allergic reactions, severe hypoglycaemia in diabetic patients and treatment failures in poorly educated or non-compliant patients.

Diagnosis

Symptoms of an acute adrenal crisis are malaise, fatigue, nausea, vomiting, abdominal pain (sometimes with peritoneal irritation), muscle pain or cramps, and dehydration leading to hypotension and shock. Impaired cognitive function, including confusion, loss of consciousness, and coma, is not uncommon. Typical laboratory findings are hyponatraemia, hyperkalaemia and increased creatinine caused by prerenal renal failure,

hypoglycaemia (in children) and sometimes mild hypercalcaemia.

Emergency measures

Treatment of patients who present in possible adrenal crisis must not be delayed by diagnostic procedures. Blood for serum cortisol, ACTH, Na, K, creatinine, urea, glucose and other testing for precipitating causes (bacterial or viral infections) should be drawn, and therapy should be initiated immediately. Rapid intravenous administration of HC (100 mg) is important to saturate HSD type 2, thereby obtaining a desired mineralocorticoid effect. Equally important is the administration of 0.9% saline (1 L over an hour) and treatment of precipitating conditions. Detailed treatment guidelines are given in Table 7. An intravenous isotonic saline infusion at a slower rate should be continued for the following 24–48 h. Parenteral glucocorticoids should be tapered over 1–3 days (if precipitating or complicating illness permits) to oral

Table 7 Treatment of acute adrenal insufficiency

Treatment	Dose/procedure
Hydrocortisone	100 mg bolus given immediately followed by 100–300 mg day ⁻¹ as continuous infusion or frequent intravenous or intramuscular boluses every 6 h
Intravenous substitution of fluids	3–4 L isotonic saline or 5 per cent dextrose in isotonic saline with an initial infusion rate of approximately 1 L h ⁻¹ ; frequent hemodynamic monitoring and measurement of serum electrolytes to avoid fluid overload
Depending on the severity of the intercurrent illness	Admission to the intensive care or high-dependency unit; prophylaxis of gastric stress ulcer; low-dose heparin; antibiotic treatment

glucocorticoid maintenance dose. Mineralocorticoid replacement with fludrocortisone should be restarted when the HC dose falls to <50 mg day⁻¹.

Prevention of further crises

To prevent future adrenal crises, it is important to diagnose the precipitating causes leading to adrenal crisis. Patient education should be reinforced to empower the patient to increase steroid doses during intercurrent illnesses, vomiting, injuries or other stressors, and the need to seek medical help before the patient reaches a state in which he/she is unable to care for him/herself. A low salt consumption and chronic under-replacement with mineralocorticoid could be causes of recurrent adrenal crises. Whether or not poor compliance and underlying psychiatric disorders may be involved should be investigated.

Guidelines for follow-up of patients with primary adrenal insufficiency

Annual follow-up

The management of PAI patients includes regular medical examinations to evaluate the biological condition of the patients, the dosage of the replacement therapy and quality of life. The goal is to obtain good appetite, stable weight, full

professional activity and/or housekeeping, and normal sexual activities.

The annual consultation should include questions regarding family relationships and professional duties, self-esteem and possible complaints due to PAI. Questions about the quality of the daily replacement therapy, self-medication during intercurrent illness and previous adrenal crises are very important to avoid such events in the future.

A physical examination is necessary to search for a possible imbalance in the physical condition of the patient. Normal skin colour is observed in the majority of patients on sufficient replacement therapy. Arterial blood pressure should be normal. Postural hypotension reflects insufficient mineralocorticoid therapy and/or low salt intake. Weight loss is a significant symptom of insufficient dosage of HC/CA, stressful situation, or additional disease of endocrine (thyrotoxicosis) or nonendocrine origin (coeliac disease).

Routine laboratory analyses include serum sodium and potassium determinations; serum and urine cortisol measurements are usually impossible to interpret. When suspecting HC under-replacement, a morning test of HC absorption and elimination could be useful, either as a cortisol serum or saliva day curve (before and 2, 4 and 6 h following the morning dose). In patients with rapid disappearance of cortisol, more frequent dosing of HC is reasonable. Assessment of PRA can be of value in patients with features of mineralocorticoid deficiency.

Screening for associated conditions

Continuous surveillance for other autoimmune disorders is necessary. The presence of thyroid autoantibodies followed by the development of hypothyroidism is frequently seen, and thyrotoxicosis may also develop. Thus, regular monitoring of thyroid function every 12 months is important, including serum TSH, FT4 and TPO-Ab. It is important to detect subclinical thyroid disease as this can contribute to fatigue. The annual screening should also include plasma glucose levels, HbA1c and a complete blood count to screen for diabetes mellitus and anaemia, respectively. B12-deficiency due to autoimmune gastritis is also common, and B12-levels should be monitored annually. In patients with frequent or episodic diarrhoea, examinations for coeliac disease (tissue

transglutaminase 2 autoantibodies and total IgA) should be performed. Women of reproductive age should be informed about the possibility of the development of POI, especially in the presence of autoantibodies against side-chain cleavage enzyme (SCC-Ab) [34].

Vitiligo and alopecia areata are frequent signs and are considered to be markers of autoimmunity. Other less frequent autoimmune disorders have to be taken into account in some patients with suggestive clinical features.

Resources for physicians and patients

Patient organizations are established in many countries, and communication by Internet helps to disseminate good practice in self-management, making the disease safer and more tolerable.

Conclusions

PAI is a potentially deadly, but treatable disease. Most cases of PAI are caused by autoimmunity and PAI patients are in particular at risk of acquiring other autoimmune diseases. Diagnosis is often delayed and many patients present with acute adrenal failure. Even when biochemical proof of PAI is evident, it is often difficult to recognize the clinical presentation. It is paramount to give immediate treatment when adrenal failure is suspected, as the diagnosis can always be established once treatment has been initiated. In most cases, the aetiologic diagnosis should be restricted to measurement of 21OH-Ab. If the patients are 21OH-Ab-negative, other causes must be investigated and excluded. Annual follow-up should include evaluation of replacement therapy, screening for associated autoimmune co-morbidities, and reiteration of emergency measures. Adrenal crises still remain a frequent cause of unnecessary deaths and urgent action taken either by the well-educated patient or healthcare providers can prevent this. Correctly treated and followed, patients with PAI can expect a near normal life expectancy, but reduced subjective health perceptions in many patients indicate that improvement in therapy is possible, which should be an aim of future research efforts.

Conflict of interests

E.S.Husebye, A. Falorni and C Betterle are members of the Plenadren International Advisory Board.

Acknowledgements

The writing of these guidelines was supported by the *Journal of Internal Medicine* and the FP7 project (Euradrenal; Grant No. 201167).

References

- 1 Erichsen MM, Lovas K, Skinningsrud B *et al.* Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. *J Clin Endocrinol Metab* 2009; **94**: 4882–90.
- 2 Soderbergh A, Winqvist O, Norheim I *et al.* Adrenal autoantibodies and organ-specific autoimmunity in patients with Addison's disease. *Clin Endocrinol* 1996; **45**: 453–60.
- 3 Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev* 2002; **23**: 327–64.
- 4 Fichna M, Fichna P, Gryczynska M, Walkowiak J, Zurawek M, Sowinski J. Screening for associated autoimmune disorders in Polish patients with Addison's disease. *Endocrine* 2010; **37**: 349–60.
- 5 Reato G, Morlin L, Chen S *et al.* Premature ovarian failure in patients with autoimmune Addison's disease: clinical, genetic, and immunological evaluation. *J Clin Endocrinol Metab* 2011; **96**: E1255–61.
- 6 Soderbergh A, Myhre AG, Ekwall O *et al.* Prevalence and clinical associations of 10 defined autoantibodies in autoimmune polyendocrine syndrome type I. *J Clin Endocrinol Metab* 2004; **89**: 557–62.
- 7 Myhre AG, Aarsetoy H, Undlien DE, Hovdenak N, Aksnes L, Husebye ES. High frequency of coeliac disease among patients with autoimmune adrenocortical failure. *Scand J Gastroenterol* 2003; **38**: 511–5.
- 8 Ghaderi M, Gambelunghe G, Tortoioli C *et al.* MHC2TA single nucleotide polymorphism and genetic risk for autoimmune adrenal insufficiency. *J Clin Endocrinol Metab* 2006; **91**: 4107–11.
- 9 Elfstrom P, Montgomery SM, Kampe O, Ekblom A, Ludvigsson JF. Risk of primary adrenal insufficiency in patients with celiac disease. *J Clin Endocrinol Metab* 2007; **92**: 3595–8.
- 10 Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. *Pediatr Ann* 1980; **9**: 154–62.
- 11 Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006; **91**: 2843–50.
- 12 Husebye ES, Perheentupa J, Rautemaa R, Kampe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. *J Intern Med* 2009; **265**: 514–29.
- 13 Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004; **350**: 2068–79.
- 14 Bjornsdottir S, Sundstrom A, Ludvigsson JF, Blomqvist P, Kampe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. *J Clin Endocrinol Metab* 2013; **98**: 2009–18.
- 15 Bjornsdottir S, Saaf M, Bensing S, Kampe O, Michaelsson K, Ludvigsson JF. Risk of hip fracture in Addison's disease:

- a population-based cohort study. *J Intern Med* 2011; **270**: 187–95.
- 16 Arlt W, Callies F, van Vlijmen JC *et al.* Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999; **341**: 1013–20.
 - 17 Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med* 1990; **322**: 1829–36.
 - 18 Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; **348**: 727–34.
 - 19 Hangaard J, Andersen M, Grodum E, Koldkjaer O, Hagen C. Pulsatile thyrotropin secretion in patients with Addison's disease during variable glucocorticoid therapy. *J Clin Endocrinol Metab* 1996; **81**: 2502–7.
 - 20 Winqvist O, Karlsson FA, Kampe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet* 1992; **339**: 1559–62.
 - 21 Meager A, Visvalingam K, Peterson P *et al.* Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Med* 2006; **3**: e289.
 - 22 Oftedal BE, Boe Wolff AS, Bratland E. Radioimmunoassay for autoantibodies against interferon omega; its use in the diagnosis of autoimmune polyendocrine syndrome type I. *Clin Immunol* 2008; **129**: 163–9.
 - 23 Ahlgren KM, Moretti S, Lundgren BA *et al.* Increased IL-17A secretion in response to *Candida albicans* in autoimmune polyendocrine syndrome type 1 and its animal model. *Eur J Immunol* 2011; **41**: 235–45.
 - 24 Sanaker PS, Husebye ES, Fondenes O, Bindoff LA. Clinical evolution of Kearns-Sayre syndrome with polyendocrinopathy and respiratory failure. *Acta Neurol Scand Suppl* 2007; **187**: 64–7.
 - 25 Falorni A, Laureti S, De Bellis A *et al.* Italian addison network study: update of diagnostic criteria for the etiological classification of primary adrenal insufficiency. *J Clin Endocrinol Metab* 2004; **89**: 1598–604.
 - 26 Mitchell AL, Pearce SH. Autoimmune Addison disease: pathophysiology and genetic complexity. *Nat Rev Endocrinol* 2012; **8**: 306–16.
 - 27 Skinningsrud B, Husebye ES, Gilfillan GD *et al.* X-linked congenital adrenal hypoplasia with hypogonadotropic hypogonadism caused by an inversion disrupting a conserved noncoding element upstream of the NR0B1 (DAX1) gene. *J Clin Endocrinol Metab* 2009; **94**: 4086–93.
 - 28 Esteban NV, Loughlin T, Yergey AL *et al.* Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* 1991; **72**: 39–45.
 - 29 Barbetta L, Dall'Asta C, Re T, Libe R, Costa E, Ambrosi B. Comparison of different regimens of glucocorticoid replacement therapy in patients with hypoadrenalism. *J Endocrinol Invest* 2005; **28**: 632–7.
 - 30 Ekman B, Bachrach-Lindstrom M, Lindstrom T, Wahlberg J, Blomgren J, Arnqvist HJ. A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency. *Clin Endocrinol* 2012; **77**: 18–25.
 - 31 Lebbe M, Arlt W. What is the best diagnostic and therapeutic management strategy for an Addison patient during pregnancy? *Clin Endocrinol* 2013; **78**: 497–502.
 - 32 Methlie P, Husebye EE, Hustad S, Lien EA, Lovas K. Grapefruit juice and licorice increase cortisol availability in patients with Addison's disease. *Eur J Endocrinol* 2011; **165**: 761–9.
 - 33 Gurnell EM, Hunt PJ, Curran SE *et al.* Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab* 2008; **93**: 400–9.
 - 34 Winqvist O, Gustafsson J, Rorsman F, Karlsson FA, Kampe O. Two different cytochrome P450 enzymes are the adrenal antigens in autoimmune polyendocrine syndrome type I and Addison's disease. *J Clin Invest* 1993; **92**: 2377–85.

Correspondence: Professor Eystein S. Husebye, Department of Clinical Science, University of Bergen, Haukeland University Hospital, N-5021 Bergen, Norway.
(fax: +47-55972950; e-mail: eyhu@helse-bergen.no). ■