Diagnosis and management of adrenal insufficiency

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Table 1. Causes of adrenal insufficiency according to underlying pathogenesis. Most frequent causes of primary adrenal insufficiency are autoimmune adrenalitis and congenital adrenal hyperplasia; secondary adrenal insufficiency is most frequently the result of hypothalamic-pituitary tumours and their treatment.

Cause	Primary adrenal insufficiency	Secondary adrenal insufficiency
Autoimmune	• Can occur in isolation or as part of autoimmune polyglandular syndromes (APS) • Isolated Addison's disease (30-40% of patients with autoimmune adrenalitis) • APS type 1 (5-10%; also termed APECED OMIM 240300): caused by *AIRE* gene mutations. Adrenal insufficiency in combination with other endocrine (hypoparathyroidism (76-93%), premature ovarian failure (17-50%), type 1 diabetes mellitus (2-12%)) and non-endocrine autoimmune disease (mucocutaneous candidiasis (73-100%), alopecia (29-37%), vitiligo (8-15%), coeliac disease (15-22%), pernicious anaemia (13-15%), autoimmune hepatitis (12-20%), Sjogren Syndrome (12%) and ectodermal dystrophy (dental enamel hypoplasia) (77-82%)) • APS type 2 (60%): adrenal insufficiency in combination with other endocrine autoimmune disease (hypo- or hyperthyroidism (60%), premature ovarian failure (7-21%),	• Lymphocytic hypophysitis – rare, may occur in relation to pregnancy. Can present as panhypopituitarism or isolated ACTH deficiency, the latter sometimes in combination with primary autoimmune-mediated hypothyroidism)

	type 1 diabetes mellitus (1-15%), pernicious anaemia (5-12%), vitiligo (6-14%), coeliac disease (1-4%), alopecia (2-6%))	
Compression / replacement of normal tissue	Bilateral adrenal metastasis (mostly originating from solid organ tumours such as lung, breast, colon cancer)	Pituitary macroadenomas (pituitary carcinoma very rare); craniopharyngioma; meningioma; ependymoma; intra- and suprasellar metastases (mostly lung, breast, colon cancer)
Infection	Tuberculosis; HIV; CMV; fungal infections	Tuberculosis; histoplasmosis; actinomycosis
Hemorrhage / necrosis /thrombosis	Thrombocytopenia; Waterhouse-Friderichsen syndrome; trauma; lupus erythematosus; antiphospholipid syndrome, panarteritis nodosa; treatment with anticoagulants; treatment with tyrosine kinase inhibitors	Pituitary apoplexy (mostly in the setting of a pituitary macroadenoma); Sheehan syndrome due to transient hypocirculation and subsequent necrosis of the pituitary (e.g. due to significant blood loss)
Infiltration	Sarcoidosis, amyloidosis, haemochromatosis, histiocytosis, lymphoma	Wegener's granulomatosis, sarcoidosis, amyloidosis, haemochromatosis, lymphoma
Surgery/ Trauma	Bilateral adrenalectomy	Treatment of hypothalamic-pituitary tumours by surgery and/or radiation; traumatic brain injury
Monogenic causes of adrenal insufficiency	Congenital adrenal hyperplasia (CAH) variants: - 21-hydroxylase deficiency (21OHD) (OMIM #201910) (most common cause of disease; >95% of CAH cases) - 11β-hydroxylase deficiency (11OHD) (OMIM #610613) - P450 oxidoreductase deficiency (PORD) (OMIM #613571) - 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD2) deficiency (OMIM #613890); - 17α- hydroxylase deficiency (17OHD) (OMIM #202110) X-linked adrenoleukodystrophy (ALD) or	Combined pituitary hormone deficiency (CPHD) variants: CPHD2 (OMIM #262600) CPHD3 (OMIM #221750) CPHD4 (OMIM #262700) CPHD5 (OMIM #182230) CPHD6 (OMIM #613986) Isolated ACTH deficiency due to mutations in TBX19 (OMIM #201400);

<table>
<tr><td></td><td>adrenomyeloneuropathy (AMN) (OMIM #300100)

APS type 1 (=APECED) (OMIM #240300)

For very rare inborn causes of primary adrenal insufficiency including congenital lipoid adrenal hyperplasia, congenital adrenal hypoplasia and familial glucocorticoid deficiency see Supplemental Table 1.</td><td>For more details on the above and even rarer inborn causes of secondary adrenal insufficiency see Supplemental Table 2.</td></tr>
<tr><td>Drugs interfering with adrenal function</td><td colspan="2">Increased metabolism of glucocorticoids: concomitant use reduces corticosteroid levels
Inducers of CYP3A4 (resulting in increased inactivation of cortisol by 6β-hydroxylation) - mitotane, phenytoin, rifampicin, troglitazone, phenobarbital
Impaired glucocorticoid action: peripheral glucocorticoid insensitivity
Glucocorticoid receptor antagonist - mifepristone (RU486)
Suppression of glucocorticoid-induced gene transcription – chlorpromazine, imipramine
Suppression of hypothalamic-pituitary-adrenal axis:
Down-regulation of endogenous ACTH release: chronic exogenous glucocorticoid administration (including topical, inhaled, oral, intra-articular or parenteral administration), megestrol acetate, medroxyprogesterone acetate, cyproterone acetate, opiates
Inhibition of steroidogenic enzymes involved in cortisol production
Inhibition of mitochondrial (type 1) cytochrome P450 enzymes (CYP11A1, CYP11B1/2): ketoconazole, fluconazole, itraconazole, etomidate, metyrapone, aminoglutethimide
Inhibition of 3β-HSD2: trilostane
Adrenal haemorrhage
Anticoagulants: heparin, warfarin
Autoimmune hypohysitis:
Anti-CTLA4 antibody: ipilimumab</td></tr>
</table>

Table 2: Measures for prevention of adrenal crisis

Action point	Intervention
Identify and define the problem	• Steroid emergency card (check that available and up to date) • Medical alert bracelet or necklace: "Adrenal insufficiency – needs steroids!"
Educate patient (and partner/parents)	**Sick day rule 1:** Need to double the routine oal glucocorticoid dose when the patient experiences fever, illness requiring bed rest or when requiring antibiotics for an infection **Sick day rule 2**: Need to inject a glucocorticoid preparation intra-muscularly or intravenously in case of severe illness, trauma, persistent vomiting, when fasting for a procedure (colonoscopy!) or during surgical intervention. Special attention to: • Explaining the rationale for dose adjustment in stress / sickness • Discussing the situations requiring dose adjustment • Discussing symptoms and signs of emergency adrenal crisis • Teaching parenteral self-administration of glucocorticoid preparation • Enforce the need to go to hospital after emergency injection
Provide patient with	• Sufficient supply of hydrocortisone and fludrocortisone (accounting for possible sick days) • Hydrocortisone emergency injection kit prescription (vials of 100 mg hydrocortisone sodium such as Solu-Cortef, syringes, needles; alternatively also hydrocortisone or prednisolone suppositories) • Leaflet with information on adrenal crisis and hospitalization to be shown to health care staff, clearly advise regarding the need to inject 100 mg hydrocortisone immediately i.v. or i.m., followed by continuous infusion of 200 mg/24 hrs • Emergency phone number of endocrine specialist team
Follow up	Re-enforce education and confirm understanding during each follow up visit (at least annually in a patient without specific problems or recent crises, otherwise more frequently)