ABSTRACT

Adrenal insufficiency continues to present a challenge for patients, their physicians and researchers. Over the last decade, long-term health outcome studies highlighted the increased rates of mortality, morbidity and impaired quality of life in patients with adrenal insufficiency. This may be at least partially due to our failure to deliver glucocorticoid replacement therapy that closely resembles physiological diurnal cortisol secretion. The potential impact of newly developed glucocorticoid preparations is a focus of current research as are the mechanisms potentially underlying the increased morbidity and mortality. Adrenal crisis remains a threat and increasing awareness and preventative measures are parts of clinical management of adrenal insufficiency that receive increasing attention.
INTRODUCTION

Adrenal insufficiency is caused by failure of the adrenal cortex to produce cortisol. This can result from loss of function of the adrenal glands, i.e. primary adrenal insufficiency, most frequently caused by autoimmune adrenalitis (“Addison’s disease”) and inborn disruption of glucocorticoid synthesis by congenital adrenal hyperplasia. Secondary adrenal insufficiency is caused by impaired hypothalamic-pituitary regulation of adrenal cortisol synthesis, mostly caused by tumours of the hypothalamic-pituitary region and their treatment by surgery or radiotherapy. However, chronic exogenous glucocorticoid treatment also invariably causes adrenal insufficiency, with potential reversibility following gradual withdrawal.

The clinical phenotype of primary adrenal insufficiency was first described by Thomas Addison in 1855, a fatal disease until corticosteroid replacement became available. Two years after Edward Kendall first isolated corticosterone in 1936, Simpson used synthetic deoxycorticosterone acetate in the treatment of Addison’s disease with success. However, widespread availability of glucocorticoids was only achieved by the synthesis of cortisone, transforming the life of patients with rheumatoid arthritis and prompting the award of the Nobel Prize in Medicine to Kendall, Philip Hench and Tadeusz Reichstein in 1950.

Today, despite these achievements, adrenal insufficiency continues to present significant challenges regarding diagnosis, optimised replacement therapy and long-term health outcomes including quality of life and mortality. This review represents a comprehensive update of our last major review, focussing on controversies and new developments.

SEARCH STRATEGY

We conducted a comprehensive search of several databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Ovid Cochrane Database of Systematic Reviews. Search terms included adrenal insufficiency, hypoadrenalism, adrenal hypofunction, Addison's disease,
adrenoleukodystrophy, and hypoaldosteronism. Case reports, letters and commentaries were excluded. We selected all relevant articles in English published from January 2003 to March 2014 to capture developments since publication of our last comprehensive review.

CAUSES OF ADRENAL INSUFFICIENCY

Causes of primary adrenal insufficiency

In developed countries, autoimmune-mediated adrenalitis with subsequent destruction of adrenal tissue is the most common cause of primary adrenal insufficiency, accounting for 68-94% of cases; it can occur in isolation (30-40%) or in combination with other autoimmune diseases as part of autoimmune polyglandular syndromes (APS) type 1 (10-15%) and type 2 (50-60%) (Table 1). APS1 (or APECED, autoimmune polyendocrinopathy with adrenal insufficiency and hypoparathyroidism, mucocutaneous candidiasis, ectodermal dystrophy) is a monogenic disease, caused by mutations in the autoimmune regulator gene AIRE, while several disease susceptibility genes have been identified for APS2 and isolated Addison’s disease (CTLA4, PTPN22, MICA)11. The latter are also associated with distinct alleles and haplotypes within the major histocompatibility complex human leukocyte antigen (HLA) including DR3-DQ2, DR4-DQ8 and DRB1 0301 and 040411.12.

The most frequent monogenic cause of adrenal insufficiency is congenital adrenal hyperplasia, which is identical in prevalence to autoimmune adrenalitis (Table 1). Congenital adrenal hyperplasia is caused by mutations in enzymes involved in glucocorticoid synthesis, most commonly (~95%) due to mutations in the CYP21A2 gene encoding 21-hydroxylase, with an incidence of 1:12,000 to 1:15,000 in most populations.

Adrenoleukodystrophy is an X-linked disorder caused by mutations in the ABCD1 gene that encodes for a peroxisomal transporter protein, resulting in defective oxidation of very long chain fatty acids and their accumulation in various tissues, most notably in brain and adrenal cortex. Clinically, adrenoleukodystrophy presents with very different phenotypes: cerebral
adrenoleukodystrophy, with childhood onset and rapid progression of neurodegeneration, and adrenomyeloneuropathy, presenting in late adolescence and adulthood with spinal and peripheral neuropathy. Adrenal insufficiency can precede neurological symptoms or even represent the only manifestation; identical mutations might result in very variable penetrance and phenotypes within affected families.

Other, rarer causes of primary adrenal insufficiency are summarised in Table 1.

Causes of secondary adrenal insufficiency

Any process destroying normal pituitary or hypothalamic tissue can lead to ACTH deficiency and consequent loss of stimulation of adrenal cortisol synthesis. Pituitary adenomas are the most frequently encountered pathology. However, other hypothalamic-pituitary tumours, such as craniopharyngiomas, meningiomas, and intra- and suprasellar metastases can also cause secondary adrenal insufficiency. Rarer causes (Table 1) are traumatic brain injury, infection and infiltration of the pituitary and all acquired and most inherited causes of secondary adrenal insufficiency can also result in loss of function of other hypothalamic-pituitary axes.

Drug-induced adrenal insufficiency

Numerous drugs can result in decreased cortisol synthesis, increased cortisol inactivation or impaired glucocorticoid action (Table 1). The most common cause of drug-induced adrenal insufficiency is the suppression of the hypothalamic-pituitary-adrenal axis by exogenous glucocorticoid doses ≥5mg prednisolone equivalent for more than four weeks, irrespective of mode of delivery (topical, inhaled, oral or injected). Similarly, patients with Cushing’s syndrome are rendered adrenal insufficient by successful treatment of the endogenous cortisol excess. Recovery of the hypothalamic-pituitary adrenal axis can take many months and time to recovery corresponds to some degree with the preceding period of glucocorticoid excess.
The enzyme CYP3A4 is responsible for metabolism of 80% of drugs and xenobiotics including all steroids. CYP3A4 inactivates cortisol to 6β-hydroxycortisol; consequently CYP3A4 inducers result in rapid inactivation of cortisol and to compensate for this, patients may require increased glucocorticoid replacement doses\textsuperscript{16}.

CLINICAL PRESENTATION

Presenting signs and symptoms in primary adrenal insufficiency are often unspecific, explaining the often significant delay in diagnosis, in many patients only established after acute hospitalization with adrenal crisis\textsuperscript{4, 17}. According to four larger series\textsuperscript{4, 11, 22, 23}, signs and symptoms comprise fatigue (84-95%), loss of appetite (53-67%), weight loss (66-76%), nausea, vomiting and abdominal pain (49-62%), and muscle and joint pain (36-40%). More specific signs and symptoms are skin hyperpigmentation (41-74%), resulting from enhanced activation of skin melanocortin 1 receptors (MC1R) by high ACTH, and salt craving (38-64%) and postural hypotension (55-68%) due to mineralocorticoid deficiency. Hyponatraemia (70-80%) is the most common laboratory abnormality, followed by hyperkalaemia (30-40%) and normochromic anaemia (11-15%)\textsuperscript{4, 10, 17}. Family history of autoimmune disease is reported by every third patient\textsuperscript{18, 19}, though rarely including Addison’s disease (generally 2%\textsuperscript{11}; 10% in Norwegians\textsuperscript{4}).

In secondary adrenal insufficiency the mineralocorticoid axis is intact, thus postural hypotension and electrolyte abnormalities are less frequent\textsuperscript{17}. However, hyponatraemia can be observed due to decreased inhibitory control of vasopressin secretion\textsuperscript{20}, effectively resulting in mild SIADH. Hyperpigmentation is absent due to reduced stimulation of skin MC1R by ACTH, giving the skin an alabaster-like appearance. In addition, other pituitary axes and also vision due to compression of the optic chiasm may be compromised.
DIAGNOSIS OF ADRENAL INSUFFICIENCY

Confirmation of Adrenal Insufficiency

The ACTH stimulation test, also termed short synacthen test or cosyntropin test, is commonly used for the diagnosis of adrenal insufficiency and can be performed at any time of the day by drawing blood for serum cortisol at baseline and 30 or 60 minutes after parenteral administration of 250µg of ACTH₁₋₂₄ (synacthen®). Some have championed the use of the so-called low dose ACTH test employing 1µg of ACTH; however, this still represents a supraphysiological stimulus and no advantage of this test has been demonstrated convincingly²¹; in addition, commercially available ACTH ampoules contain 250µg ACTH₁₋₂₄, rendering a dilution impractical and too inaccurate for routine use.

Cortisol response to ACTH is slightly higher at 60 than at 30 min²², but there are no documented advantages in sensitivity and specificity for the use of either time-point. The exact diagnostic cut-offs depend on assay-specific local reference ranges and are usually set at 500-550 nmol/L (18-20 µg/dl) after ACTH stimulation.

Cortisol secretion follows a characteristic diurnal rhythm, rising in the early morning hours (2-4am), peaking in the morning (6-9 a.m.) and then descending to low levels in the evening and very low levels around midnight²³. Random morning cortisol levels <80nmol/L (3µg/dl) are strongly predictive of adrenal insufficiency²⁴. However, to safely establish the diagnosis of adrenal insufficiency, an ACTH stimulation test should always be performed. Importantly, diagnostic tests should never delay the prompt initiation of life-saving hydrocortisone treatment in suspected adrenal crisis; formal confirmation of diagnosis can be safely carried out after clinical recovery.

Measurement of plasma ACTH is the mandatory first step in the differential diagnosis of adrenal insufficiency (Figure 1). In primary adrenal insufficiency, ACTH levels are usually >100pg/mL (22pmol/L)²⁵; plasma renin will also be elevated, with concomitantly low serum aldosterone. In secondary adrenal insufficiency, ACTH levels will be low or inappropriately normal while
mineralocorticoid secretion is sufficient. Serum DHEAS will be invariably low in both primary and secondary adrenal insufficiency.

In secondary adrenal insufficiency, where adrenal atrophy ensues from lack of endogenous ACTH stimulation, the short synacthen test is also generally useful. However, within four weeks of a pituitary insult/surgery the adrenal glands are not yet atrophied and thus will still be responsive to ACTH, which could wrongly indicate an intact HPA axis. Early postoperative morning cortisol levels >275nmol/L (10µg/dl) were shown to be an accurate predictor of a normal corticotroph reserve\textsuperscript{26,27}. The long-term predictive value of short synacthen test cut-offs of 510 and 550nmol/L were evaluated retrospectively in a large cohort of patients investigated for secondary adrenal insufficiency and demonstrated a very low incidence of false negative results (2/178 patients)\textsuperscript{28}.

The insulin tolerance test is the gold standard for diagnosis of secondary adrenal insufficiency but the testing procedure is cumbersome, expensive to carry out and can be unsafe in patients with history of seizures and cardiac disease; special care should be taken if the test is carried out in children or elderly patients. Achieving or failing to achieve an adequate hypoglycaemia (2.2 mmol/L (<40 mg/dl)) are additional limiting factors. Usually 0.1U insulin per kg body weight is used, however around a third of patients need more\textsuperscript{29}. Peak cortisol levels <500nmol/L (18µg/dl) are considered diagnostic for adrenal insufficiency\textsuperscript{30}.

**DIFFERENTIAL DIAGNOSIS AND CONFIRMATION OF ETIOLOGY**

In primary adrenal insufficiency, increased antibody titres against 21-hydroxylase and adrenal cortex are indicators of autoimmune adrenalitis\textsuperscript{31}, the most frequent cause of disease once congenital adrenal hyperplasia is ruled out. Therefore measurement of relevant auto-antibodies is the logical first step in differential diagnosis. If neither the family history nor antibody titre point toward autoimmune pathogenesis, then further investigations should be undertaken (Figure 1).
However, autoimmune adrenalitis is still the most likely underlying cause as many patients turn antibody negative when autoimmune destruction has progressed for some time.

Screening for congenital adrenal hyperplasia in adults with adrenal insufficiency consists of serum 17-hydroxyprogesterone at baseline and after ACTH. In antibody-negative patients, adrenal imaging is helpful and can reveal infiltrative processes, infection or haemorrhage. Bilateral metastases of solid organ tumours such as lung, breast and kidney are associated with an increased risk of adrenal insufficiency; therefore such patients should undergo screening by a short synacthen test. In antibody-negative men, screening for plasma very long chain fatty acids should be carried out, to exclude adrenoleukodystrophy, even if no neurological signs are present. In secondary adrenal insufficiency, MRI imaging of the hypothalamic-pituitary area is the first point of call. Pituitary incidentalomas are frequent and unlikely to cause adrenal insufficiency unless >1 cm; thus pituitary imaging is only warranted if plasma ACTH is low or inappropriately normal and cortisol fails to respond appropriately to ACTH. Review of medications should include recent use of topical and intra-articular corticosteroid preparations and over-the-counter supplements.

SPECIAL DIAGNOSTIC SITUATIONS

Adrenal crisis, hospital admission: If acute adrenal insufficiency is clinically suspected, hydrocortisone should be administered without delay (100mg bolus injection, followed by 200mg per 24 hours either as a continuous infusion or 50mg every 6 hours) along with intravenous fluid resuscitation. If possible, blood samples for paired cortisol and ACTH can be drawn beforehand and in haemodynamically stable patients also a short synacthen test can be performed; however, if in doubt, it is better to treat promptly and confirm the diagnosis later after the patient is better.

Increased or reduced corticosteroid-binding globulin concentrations: More than 90% of circulating cortisol is bound to corticosteroid binding globulin (CBG) and only the remaining free fraction is biologically active. Although not routinely advocated, there are special circumstances
in which measurement of serum free cortisol and/or CBG may be useful. CBG is decreased during acute illness, in severe liver disease and in the rare patients with CBG gene mutations. Enhanced oestrogen action, e.g. during pregnancy or intake of oral contraceptives, significantly increases CBG, resulting in increased total cortisol but unchanged free cortisol. The latter is not routinely measured and studies on normal reference values in pregnancy are currently lacking. Data on the utility of salivary cortisol are too limited for firm recommendations\textsuperscript{34,35}.

**Patients on exogenous steroids:** Current or recent exogenous glucocorticoid therapy can complicate interpretation of ACTH test results. Careful review of treatment history during the last 12 months (including administration of topical, inhaled, intranasal, epidural or intra-articular preparations) is essential. A further important consideration is the possibility that some synthetic glucocorticoids can cross-react with the immunoassays used to measure circulating cortisol in many routine biochemistry laboratories\textsuperscript{36}.

Assessing the adequacy of adrenal reserve in patients who are undergoing planned withdrawal of chronic exogenous glucocorticoid treatment can be challenging\textsuperscript{37}. Supraphysiological glucocorticoid therapy causes adrenal atrophy that is slowly reversible in the majority of cases. However, there is considerable inter-individual variability in the degree of hypothalamic-pituitary-adrenal axis suppression and the time to recovery\textsuperscript{14}. Glucocorticoids should be slowly tapered and if there is no ongoing indication for glucocorticoid therapy other than adrenal insufficiency, long-acting glucocorticoids should ideally be switched to hydrocortisone. Assessment of adrenal function can be undertaken after hydrocortisone has been temporarily stopped for 24 hours prior to ACTH\textsubscript{1-24} stimulation testing. Prednisone, prednisolone and dexamethasone may impact on results for at least 48-72 hours if not longer, hence switching to hydrocortisone prior to comprehensive testing of adrenal reserve is often more prudent.

All modes of glucocorticoid administration (oral, inhaled, intranasal, topical, intra-articular, intramuscular and intra-venous) have been associated with hypothalamic-pituitary-adrenal axis suppression, which may be present in half of the patients taking inhaled glucocorticoid therapy\textsuperscript{38-}.
though the true magnitude of this problem and the clinical consequences are still largely unknown and data on optimised diagnostic work-up are limited. If there are signs and symptoms suggestive of adrenal insufficiency, dynamic assessment of adrenal reserve should be undertaken, but routine screening in all patients on inhaled, topical or intranasal therapy is not recommended. Often, it is not possible to omit glucocorticoid therapy, even for a short period of time (inhaled glucocorticoids for asthma), further complicating the assessment. It is important to take a multidisciplinary team approach to clarify whether supraphysiological glucocorticoid therapy is still required or whether glucocorticoids can be carefully tapered. Management can be complex and a balance between the prevention of adrenal crisis and minimizing glucocorticoid excess.

**CHRONIC REPLACEMENT THERAPY**

Glucocorticoid replacement

Daily physiological production of cortisol is around 5-6 mg/m² body surface area⁴¹. Currently recommended hydrocortisone doses are 15-25 mg, usually administered in two to three daily doses, with 50-66% of the daily dose administered in the morning upon awakening⁹. The second dose is usually administered 6-8 hours after the morning dose; if a thrice daily regimen is followed the second dose is administered 4-6 hours after the early morning dose and the third dose 4-6 hours thereafter. Some recommend weight-adjusted dosing to achieve reduction in intervals of excess in cortisol levels during the day and decreased variability of cortisol profiles⁴². Decision on number of doses is also based on patient preference, differences in daily activity and experience.

As there is no reliable biochemical marker to assess the appropriateness of glucocorticoid replacement dose, dose modification is guided by clinical judgment, subjective perception of symptoms and signs and symptoms of glucocorticoid under- and over-replacement, respectively. The goal is to achieve the best clinical result with the lowest possible daily dose of steroid. Cortisol day curves are of limited value in routine monitoring⁴³. In our experience, timed
measurement of serum cortisol is only of value if malabsorption or increased metabolic clearance is suspected. Monitoring plasma ACTH is not useful. Urinary 24-h free cortisol excretion shows considerable inter-individual variability and comparison to normal reference ranges are not useful as due to the pharmacokinetic properties of current glucocorticoid preparations the kidney excretion threshold is much more quickly overcome after exogenous administration of glucocorticoids.

A global survey of more than 1000 patients with mostly primary adrenal insufficiency revealed that hydrocortisone is most commonly used (75%), followed by prednisone/prednisolone (11%), cortisone acetate (6%) and dexamethasone (4%)\textsuperscript{44}. Cortisone acetate (1.6 hydrocortisone equivalent) and prednisone (0.25 hydrocortisone equivalent) require intrahepatic activation to cortisol and prednisolone (0.20mg hydrocortisone equivalent), respectively, by 11β-hydroxysteroid dehydrogenase type 1, which might lead to a higher pharmacokinetic variability compared to hydrocortisone. The long-lasting synthetic steroids prednisone and dexamethasone (0.025 hydrocortisone equivalent) exert strong anti-inflammatory action and hence are frequently used in chronic inflammatory conditions.

Over the last few years progress has been made in the development of steroid preparations aiming to provide a more circadian-based serum cortisol profile\textsuperscript{23}. This was pioneered by the demonstration of superior biochemical control as well as indications of improved quality of life in adrenal insufficiency patients receiving intravenous and subcutaneous hydrocortisone infusions\textsuperscript{45}. An approved option for modified release oral hydrocortisone is Duocort that provides longer acting delivery of hydrocortisone, however, fails to resurrect physiologic early morning secretion of cortisol. An early rise in morning cortisol can be achieved by modified and delayed release glucocorticoid preparations, such as prednisone delayed-release tablets and, possibly more physiologically, by the modified and delayed release hydrocortisone preparation Chronocort that is currently under development\textsuperscript{23, 46}. However, data from larger clinical trials on the beneficial impact of these newer preparations in patients with adrenal insufficiency are currently still
lacking. We recommend an individualized approach based on clinical symptoms and signs, patient’s circumstances and preferences.

Mineralocorticoid replacement

Fludrocortisone (9-alpha-fluor-cortisol) is used for mineralocorticoid replacement as a single morning dose, usually between 50-300µg, with a typical starting dose of 100-150µg. Electrolytes within the normal range, blood pressure without a significant postural drops and plasma renin concentrations/activity in the upper normal range serve as indicators of adequate mineralocorticoid replacement. Hydrocortisone also exerts mineralocorticoid activity, with 40mg hydrocortisone equivalent to 100µg fludrocortisone. Thus, changes in hydrocortisone dose may impact on fludrocortisone dose requirements. Prednisolone has some and dexamethasone has absolutely no mineralocorticoid activity.

Fludrocortisone requirements are monitored by serum sodium and potassium and plasma renin, the latter should range in the upper normal reference range. The presence of salt craving, dizziness and postural hypotension could be indicative of underreplacement, while peripheral oedema and new-onset arterial hypertension could indicate overreplacement. Fludrocortisone dose requires increasing in ease of enhanced salt loss through perspiration, e.g. due to physical activity or a hot climate.

Adrenal androgen precursor replacement:

In women, androgen production by the adrenal glands is the main source of androgens; therefore, adrenal insufficiency is invariably associated with severe androgen deficiency in women. Serum DHEAS concentrations physiologically peak between 20-30 years, followed by a gradual decline that is independent of menopause. The adrenal androgen precursor dehydroepiandrosterone, DHEA, is activated to sex steroids in a wide variety of peripheral tissues and in the gonads, but has also neurosteroidal activity in the brain. DHEA supplementation in
adrenal insufficiency has been shown to improve overall wellbeing\textsuperscript{48-51}, depression and anxiety scores\textsuperscript{48,52} and sexual interest and satisfaction\textsuperscript{48} in some trials, but not all. The benefit of DHEA replacement is likely to be more significant in women of premenopausal age\textsuperscript{51}. A trial of DHEA could be considered in particular in women with adrenal insufficiency and otherwise optimised glucocorticoid and mineralocorticoid replacement who suffer from low energy levels, impaired mood and decreased or absent libido. Single oral administration of 25-50 mg DHEA usually restores circulating androgen levels into the normal range. Monitoring comprises serum DHEAS, androstenedione, testosterone and SHBG 24 hours after the last morning dose, aiming at mid normal range levels. At present, studies on long-term outcomes of chronic DHEA supplementation in hypoadrenal women are lacking and are unlikely to be available soon as the steroid is widely available over the counter and the internet.

Regenerating adrenal function

Novel therapies beyond optimisation of steroid replacement therapy is a subject of current research and published approaches include immunosuppressive treatment in early stage Addison’s\textsuperscript{53} as well as attempts to achieve adrenal transplantation\textsuperscript{54}. Most recently, a proof-of-principle study showed re-emergence of adrenal function after continuous ACTH stimulation with depot synacthen in two patients with chronic Addison’s disease but minor residual function\textsuperscript{55}.

Special therapeutic situations

Various environmental, physiologic and pathologic conditions may influence replacement therapy in patients with adrenal insufficiency. Little evidence exists to suggest an optimal approach in these situations and the recommendations below represent expert opinion.

\textbf{Shift work or otherwise shifted daily routine (adolescents, students):} We recommend changing the timing of steroid replacement according to the individual schedule (to take the larger dose of hydrocortisone on waking and the second dose in 6-8 hours after the first one).
Intensive exercise: Small carbohydrate meals before intense exercise bouts can be considered but are not mandatory and depend on individual response. Depending on the degree of physical activity and thus expected salt losses by sweating, the patient might benefit from a small dose increase in both glucocorticoid and mineralocorticoid, e.g. 2.5-5.0mg hydrocortisone every three hours during a marathon, and in a hot environment increasing fludrocortisone dose by 50-100µg per day to compensate for salt and water loss has been recommended.

Arterial hypertension: If a patient with primary adrenal insufficiency develops hypertension, the appropriateness of fludrocortisone dose should be checked; however, also Addison patients can develop essential hypertension. In this situation a slight reduction of fludrocortisone dose can be considered, tolerating slightly elevated renin levels, but mineralocorticoid treatment should not be stopped altogether and if needed, appropriate antihypertensive treatment should be established, preferably using calcium antagonists and alpha-blockers. ACE inhibitors and AT1R blockers are ineffective as the renin-angiotensin-aldosterone system is already disrupted.

Diabetes mellitus: Newly developed type 2 diabetes should prompt consideration of the appropriateness of glucocorticoid dose. In patients with insulin-dependent diabetes mellitus, longer-acting glucocorticoids might help to achieve better glucose controls.

Thyroid dysfunction: Hyperthyroidism increases cortisol clearance, thus thyrotoxic patients with adrenal insufficiency require higher hydrocortisone replacement doses. New onset hyperthyroidism can elicit an adrenal crisis; L-thyroxine replacement should only be initiated after hydrocortisone replacement has already been established. TSH levels <10mU/L in newly diagnosed Addison patients may not indicate hypothyroidism as TRH release physiologically requires inhibitory control by cortisol; therefore, TSH often normalises with hydrocortisone replacement alone.

End-stage renal disease: In patients requiring dialysis, fludrocortisone is no longer needed and can be stopped; it is important to plan daily glucocorticoid replacement considering the fact that significant amounts of the morning glucocorticoid dose may be lost through haemodialysis.
Treatment and prevention of acute adrenal crisis

Adrenal crisis represents a life-threatening emergency. Therefore, prevention is of key importance. The frequency of crisis has been reported as 6-8/100 patient years, with around a half of patients with Addison’s disease reporting at least one previous adrenal crisis. Most frequent precipitating causes are gastroenteritis and fever (60-70%), but also other stressful events such as trauma, surgery, dental procedure and also major psychological distress. Many crises result from failure to adjust glucocorticoid dose appropriately or at all; this is also caused to a significant degree by limited knowledge and slow reaction time of physicians involved in the acute care of adrenal insufficiency patients with incipient crisis. Patients with other comorbidities such as diabetes mellitus, diabetes insipidus, asthma and premature ovarian failure are at higher risk, but this does not sufficiently discriminate those patients with increased risk of adrenal crisis. Symptoms include fatigue, nausea, vomiting, abdominal pain, muscle cramps, hypotension and can accelerate to hypovolaemic shock and coma. Hyponatraemia, hyperkalaemia and prerenal failure are frequently noted; hypoglycaemia is rarely observed in adults, but relatively frequent in children in whom it can significantly affect neurological outcome.

Treatment includes prompt rehydration (1000ml of physiological saline in the first hour, 500 ml in the second hour followed by continuous fluid administration) and immediate parenteral administration of 100 mg hydrocortisone, followed by 200mg/24h, ideally per continuous i.v. infusion, alternatively in three to four daily doses per i.v. or i.m. injection. Patients require monitoring of vital signs and regular assessment of serum electrolytes. If clinically stable, glucocorticoid dose can be quickly tapered to the normal maintenance dose over 24-72 hours. Mineralocorticoid administration should be initiated as soon as total daily hydrocortisone dose is less than 50mg.

Adequate prevention and treatment of adrenal crisis are of highest importance to avoid fatal outcomes. As adrenal insufficiency is a rare disease, many physicians are not familiar with its management often resulting in critical delays in emergency treatment. Education of patients and
relatives must provide information on correct adjustment of glucocorticoid replacement (sick day rules), symptom awareness, and steroid emergency card and medical alert bracelets (Table 2). The development and Europe-wide roll out of a steroid emergency card aiming to encourage the treating physician to immediately administer hydrocortisone in case of imminent crisis is currently under way.

Emergency self-administration of hydrocortisone is of key importance to prevent crisis-related morbidity and mortality. In a 2006 survey 66% of Addison patients reporting a crisis had relied on medical personnel to administer the first treatment; only 12% of patients self-administered a hydrocortisone injection, with another 17% treated by a close person. Almost a third of patients did not have an emergency injection kit. As an alternative to intramuscular injection, which some patients are hesitant to administer promptly, subcutaneous injections might be an alternative, generating similar pharmacokinetics to intramuscular injection. Suppositories containing 100 mg of prednisolone can be used based on patient’s preference. Progress in this area will be achieved once pharmaceutical companies make progress in the development of a suitable self-injection device similar to the epinephrine auto-injector for patients with anaphylaxis.

FERTILITY AND PREGNANCY

Women with Addison’s disease have reduced rates of fertility, even after exclusion of women with premature ovarian failure. An increased risk of miscarriage has also been reported. Women with Addison’s disease also suffer higher rates of preterm birth and Caesarean delivery and more likely to have newborns with low birth weight (<2500g). While women with adrenal insufficiency due congenital adrenal hyperplasia may often require Caesarean delivery, if there was previous genital correction surgery, other women with adrenal insufficiency should not require Caesarean delivery any more frequently than women in the normal population.
Physiologically, total cortisol concentrations are 2-3 times increased in pregnancy\textsuperscript{65}, rising in the first trimester due to higher CBG levels and increased cortisol half-life secondary to decreases in hepatic clearance of the bound hormone\textsuperscript{66}. However, from the 22\textsuperscript{nd} week of gestation onwards also free cortisol levels increase significantly, most likely due to increased placental production of CRH. This results in hypertrophy of adrenal glands and increased responsiveness to synacthen as the pregnancy progresses\textsuperscript{35,67}, with diagnostic and therapeutic implications.

Adrenal insufficiency symptoms overlap with symptoms that might be related to pregnancy itself, such as fatigue, hyponatraemia, nausea and vomiting. The short synacthen stimulation test remains the test of choice in pregnant women if adrenal insufficiency is suspected. In a small cohort of healthy pregnant women the peak total cortisol response after ACTH injection was significantly higher in comparison to the non-pregnant state (median of 1000 nmol/L (37 µg/dl) in the second and third trimester versus 700 nmol/L (26 µg/dl) postpartum)\textsuperscript{35}. Thus, it is prudent to use higher total cortisol cut-offs for confirming a diagnosis of adrenal insufficiency until more data is available; diagnostic cut-offs of 700nmol/L (25µg/dl), 800nmol/L (29µg/dl) and 900nmol/L (32µg/dl) for the first, second and third trimester, respectively, have been recommended\textsuperscript{68}. Although adrenal crisis due to failing to adapt the dose of glucocorticoid during pregnancy has been reported\textsuperscript{59}, little evidence exists on the optimal glucocorticoid replacement during pregnancy\textsuperscript{84}. Our usual practice is to increase hydrocortisone dose by around 20-40% during the third trimester to reflect the physiologic increase in free cortisol.

Clinical assessment of mineralocorticoid requirements during pregnancy is difficult, again due to overlapping unspecific symptoms, such as oedema or postural hypotension. Sodium and potassium can be monitored in blood and urine; however plasma renin is not informative as levels physiologically increase during pregnancy. Increasing progesterone levels during pregnancy exert an anti-mineralocorticoid effect, thus it is sometimes required to adjust fludrocortisone dose\textsuperscript{69}.

During delivery hydrocortisone replacement should be similar to that in major surgical stress; 100mg hydrocortisone i.v. at the onset of active labour (cervix 4 cm and/or contractions every 5
min for one hour), followed by hydrocortisone 200mg/24h per continuous i.v. infusion (or 50mg hydrocortisone i.v. or i.m. every six hours) until after delivery; thereafter, hydrocortisone can be quickly tapered back to pre-pregnancy doses within two to four days\textsuperscript{57}.

SUBJECTIVE HEALTH STATUS
Patients with both primary and secondary adrenal insufficiency report reduced quality of life (QoL) in comparison to healthy controls; this is still observed even in patients with isolated adrenal insufficiency without any comorbidity. This finding corresponds with a higher level of working disability compared to the general population\textsuperscript{3, 4, 70} It has been shown that an inverse relationship of QoL and the age of adrenal insufficiency onset exists. Female sex, comorbidities and a delayed diagnosis of adrenal insufficiency were also noted as risk factors for decreased QoL\textsuperscript{17}. The reduction in QoL despite established replacement therapy might be related to glucocorticoid over- or under-replacement, non-physiological circadian cortisol pattern generated by the currently available hydrocortisone preparations\textsuperscript{71, 72} or to lack of adrenal androgen replacement\textsuperscript{48, 51}, indicating in principle an urgent need for improved replacement strategies\textsuperscript{73}. In retrospective analyses, QoL was negatively correlated with the glucocorticoid dose and was still reduced in patients receiving DHEA replacement\textsuperscript{70}. This suggests that non-physiological glucocorticoid replacement may play a major role. A small study restoring the circadian profile by administration of hydrocortisone via insulin pump demonstrated an increase of QoL\textsuperscript{74}. Convincing data on optimal interventions in order to improve QoL however, is still lacking despite growing interest.

PROGNOSIS
In general, the prognosis for appropriately diagnosed and treated patients with adrenal insufficiency is good. However, it remains a potentially lethal condition and adrenal crisis remains one of the frequent causes of death, in particular in younger patients\textsuperscript{75}. Standardized
mortality rates are more than double that of the age and sex adjusted control population in both primary and secondary adrenal insufficiency patients\textsuperscript{5, 76-78}. Increased mortality in primary adrenal insufficiency is linked to increased rate of mainly respiratory infections \textsuperscript{77} and, in particular in patients <40 years, also to adrenal crisis and sudden death\textsuperscript{74}.

In clinical practice, a significant proportion of patients regularly take replacement doses that are in excess of normal physiological levels, often to try to alleviate many of their symptoms. In addition, previous over-estimates of physiological cortisol production rates may have led to prescribed doses in excess of physiological requirements\textsuperscript{79}. Furthermore, patients often take extra doses of hydrocortisone. For example, 52\% of patients with adrenal insufficiency reported taking extra doses 1-3 times a month and 20\% took extra doses more often\textsuperscript{4}. Supraphysiological glucocorticoid replacement is associated with increased mortality\textsuperscript{80}, cardiovascular risk and bone fragility. There is a clear HC dose response with BMI, triglyceride and total and LDL cholesterol concentrations in hypopituitary patients. However, all patients taking 20mg or less of HC per day had metabolic profiles similar to those with intact HPA axis\textsuperscript{81}. A higher prevalence of central adiposity, impaired glucose tolerance and dyslipidaemia has been observed in patients with Addison’s disease taking 30mg hydrocortisone\textsuperscript{82}. Interestingly, a more adverse metabolic response was noted when hydrocortisone was administered in the evening\textsuperscript{83}. Studies have also shown an increased incidence of osteoporosis in patients receiving >30 mg of HC or 7.5 mg prednisone per day\textsuperscript{43, 84} and an increased risk of fractures in Addison patients\textsuperscript{85}. However, currently recommended replacement doses of 15-25 mg per day do not affect bone density\textsuperscript{86}.

In conclusion, despite significant advances over the last decade, the diagnosis and management of adrenal insufficiency still presents challenges and requires consideration of special situations to tailor replacement therapy to the individual patient. Raising awareness and education of both medical teams and patients on adrenal insufficiency and management of adrenal crisis is of paramount importance to improve clinical outcome. It remains to be demonstrated whether
modified release hydrocortisone preparations will provide a novel avenue for more physiologic replacement able to improve quality of life and prevent metabolic consequences.

Contributors:

All authors participated in the literature search, manuscript writing and editing, and the design of tables and figures. The corresponding author (W.A.) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of Interest:

W.A. acts as a consultant to Diurnal Ltd., S.H. serves as a consultant for Viropharma, J.W.T. and I.B. have no conflicts of interest.
Figure legend

**Figure 1:** Diagnostic algorithm for adults with clinical signs and symptoms suggestive of adrenal insufficiency. Diagnostic measures should never delay the initiation of hydrocortisone treatment in suspected adrenal crisis.
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27


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