

# Adrenal insufficiency

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## ABSTRACT

Adrenal insufficiency (AI), first described by Thomas Addison in 1855, is characterised by inadequate hormonal production by the adrenal gland, which could either be primary, due to destruction of the adrenal cortex, or secondary/tertiary, due to lack of adrenocorticotropic hormone or its stimulation by corticotropin-releasing hormone. This was an invariably fatal condition in Addison's days with most patients dying within a few years of diagnosis. However, discovery of cortisone in the 1940s not only improved the life expectancy of these patients but also had a dramatic effect on their overall quality of life. The diagnosis, easily confirmed by demonstrating inappropriately low cortisol secretion, is often delayed by months, and many patients present with acute adrenal crisis. Sudden withdrawal from chronic glucocorticoid therapy is the most common cause of AI. Currently, there remains a wide variation in the management of this condition across Europe. As primary AI is a relatively rare condition, most medical specialists will only manage a handful of these patients in their career. Despite many advances in recent years, there is currently no curative option, and modern cortisol replacement regimens fail to adequately mimic physiological cortisol rhythm. A number of new approaches including allograft of adrenocortical tissue and stem cell therapy are being tried but remain largely experimental.

## INTRODUCTION

The adrenal glands, a pair of triangular glands that sit atop the kidneys, are vital for survival, and bilateral adrenalectomy, in the absence of adrenocortical hormones replacement, is not compatible with life for more than a few days.<sup>1</sup> An adrenal gland is made of cortex, the outer region divided into three separate zones: zona glomerulosa (secreting mineralocorticoids such as aldosterone), zona fasciculata (secreting glucocorticoids such as cortisol) and zona reticularis (secreting androgens such as dehydroepiandrosterone (DHEA)), and medulla, which produces stress hormones including epinephrine.<sup>2</sup>

Adrenal insufficiency (AI) is a relatively rare but serious condition characterised by reduced production of glucocorticoids and/or mineralocorticoids and adrenal androgens due to the destruction of the adrenal gland or lack of its stimulation. It can be divided into primary adrenal insufficiency (PAI), secondary adrenal insufficiency (SAI) and tertiary adrenal insufficiency (TAI), depending on whether the disease process affects the adrenal cortex, anterior pituitary gland or the hypothalamus, respectively (figure 1). The condition presents with subtle and rather non-specific signs and symptoms that develop over weeks and months and

is often missed, leading to a delay in diagnosis; as such, a high level of clinical suspicion is required to make the diagnosis. Patients may occasionally present with life-threatening complications as the first manifestation of condition, and the impact of this condition depends on the speed with which the condition develops, the nature of stressful trigger and the patient's background medical condition.

A number of advances have been made over the past several decades in the management of AI, but treatment often remains suboptimal even after the diagnosis is made, which leads to impaired quality of life<sup>3</sup> and increased mortality.<sup>4</sup>

## EPIDEMIOLOGY

PAI (due to defect at adrenal level) is a rare disease with reported numbers rising from 40 to 70 cases per million in Europe in the 1960s<sup>5</sup> to about 100–140 cases per million at the beginning of this century.<sup>6</sup> Interestingly, this trend seems to be continuing,<sup>7</sup> which could well be due to improved diagnostics over time and increased awareness among physicians.<sup>8</sup> Although it can present at any age, most patients present between 30 and 50 years and it affects women more frequently than men.

SAI (due to defect at pituitary level) is more common<sup>9</sup> with an estimated prevalence of 150–280 per million and is also more common in women than men. Affected patients are mostly diagnosed in the sixth decade of life.<sup>10</sup>

TAI (due to defect at hypothalamic level, mostly caused by exogenous steroid treatment) is the the most common type and is easily missed as the symptoms may be indistinguishable from those of the underlying condition for which patient is taking steroids.<sup>11</sup> Any disease involving the hypothalamus that interferes with corticotropin-releasing hormone (CRH) secretion will result in TAI.

## CAUSES OF AI

PAI, commonly known as Addison's disease,<sup>12</sup> may be inherited or acquired. The most common *inherited* form of PAI is congenital adrenal hyperplasia (CAH), which refers to a group of genetic disorders that disrupt adrenal steroidogenesis.<sup>13</sup> More than 95% of cases of CAH (1: 10 000–18 000 births) are caused by a recessive mutation in the CYP21A2 gene, which codes for 21-hydroxylase, a key enzyme in cortisol and aldosterone biosynthesis. A comprehensive review of CAH is beyond the scope of this article and will not be discussed here.

*Acquired* PAI is caused primarily by autoimmune adrenalitis (immune system targeting 21-hydroxylase), which constitutes 70%–80% of all cases in the Western world and can occur in isolation (40%) or as a component of autoimmune polyendocrinopathy syndrome (APS) (60%).<sup>14</sup> It is

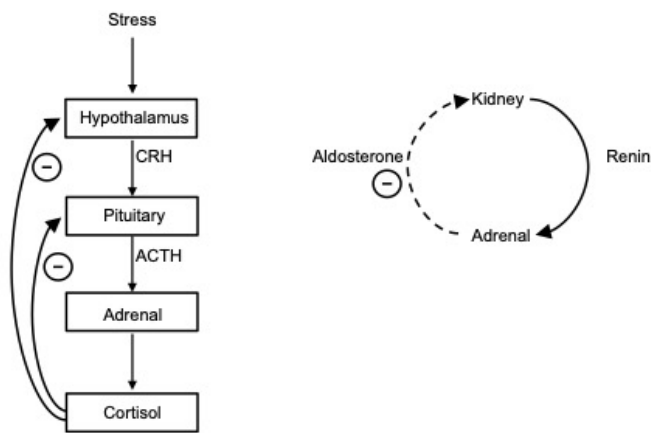


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**Figure 1** Simplified scheme of control of cortisol and aldosterone production. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

thought that a viral infection or an exaggerated body response to an inflammatory signal, in a genetically susceptible individual, starts an autoimmune cascade, which eventually leads to AI. The first sign of an ongoing autoimmune process is the presence of autoantibodies against 21-hydroxylase, which can be found in about 90% of cases, and detection of these antibodies is diagnostic of PAI. They, however, serve only as biological markers of autoimmunity and have no direct role in pathogenesis of AI.<sup>15</sup>

However, infectious diseases such as tuberculosis and fungal infections are important causes in low-income countries.

SAI presents either due to deficient adrenocorticotropic hormone (ACTH) secretion as an isolated defect or in combination with other pituitary hormones deficiency with pituitary adenoma being the most common cause.<sup>10</sup>

Finally, TAI is most commonly iatrogenic, caused by sudden withdrawal from long-term exogenous steroid use.<sup>11</sup> A number of factors can influence the risk of TAI including the dose, duration, half-life, potency and route of administration of glucocorticoid. Moreover, drugs that affect the glucocorticoid metabolism may also alter the risk of TAI.<sup>16</sup> Patients on bedtime glucocorticoid and on multiple split doses are more likely to have hypothalamic–pituitary–adrenal (HPA) suppression due to adverse effect on circadian ACTH rhythm.<sup>17</sup> On the other hand, patients on alternate day regime and those on pulse steroid regime with high-dose systemic glucocorticoids are less likely to suffer from TAI as HPA axis would have had time to recover.<sup>18</sup>

Opiates induced AI, an underappreciated side effect of chronic opiate therapy, due to central suppression of the HPA axis leading to TAI, which has been reported in as many as 29% of patients. It is dose related and is more likely to occur in individuals on high-dose opiates.<sup>19</sup>

Common causes of AI are listed in [table 1](#).

**PATHOPHYSIOLOGY OF AI**

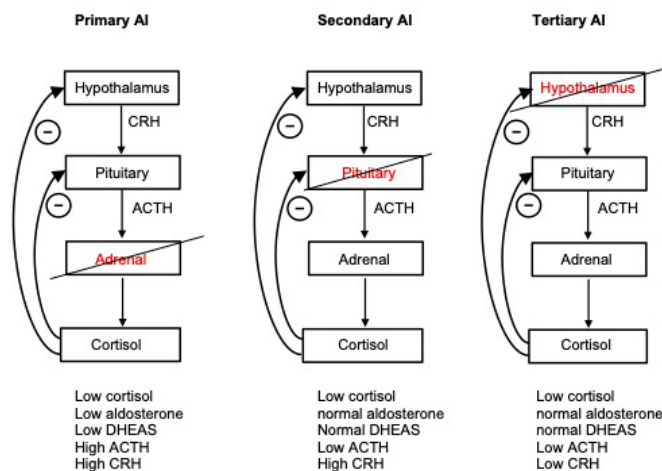
The HPA axis, with endogenous cortisol exerting strong negative feedback at the hypothalamic and pituitary levels, describes the close interaction between these three endocrine organs.<sup>20</sup> It gets stimulated by and prepares the body to cope with stressful stimuli and tightly regulates the secretion of cortisol in a circadian and ultradian (pulsatile with a frequency of 3–6 hours) rhythm. Cortisol deficiency in PAI results in elevated levels of plasma ACTH and CRH due to loss of negative feedback ([figure 2](#)).

**Table 1** Common causes of AI

Primary AI	
Autoimmune	Isolated, autoimmune polyendocrinopathy syndrome types 1 and 2
Infection	Tuberculosis, HIV, fungal, viral
Others	Bilateral adrenal haemorrhage, adrenal metastasis, adrenal infiltration, bilateral adrenalectomy, drug induced
Genetic	Adrenoleukodystrophy, congenital adrenal hyperplasia, adrenal hypoplasia congenita, adrenocorticotropic hormone, insensitivity syndromes
Secondary AI	
Space occupying lesions/trauma/surgery	Pituitary tumours, trauma, surgery, irradiation
	Infection or infiltration affecting anterior pituitary, pituitary apoplexy, Sheehan’s syndrome, drugs
Tertiary AI	
Space occupying lesions/trauma/surgery	Hypothalamic tumours, trauma, surgery, irradiation
Drug induced	Glucocorticoid, opiates
AI, adrenal insufficiency.	

Secretion of adrenal mineralocorticoid aldosterone is regulated mainly through the renin–angiotensin system or dietary potassium. Lack of adrenal mineralocorticoid leads to increased renin release by the juxtaglomerular cells of the kidneys. ([figure 1](#)). ACTH does not play a significant role in the long-term regulation of mineralocorticoid secretion, although it does stimulate aldosterone secretion in an acute and transient fashion but to a lesser extent than angiotensin II and potassium.<sup>21</sup>

In PAI, the loss of adrenal cortex is gradual, and symptoms and signs of AI do not appear until at least 90% of adrenal cortex is lost.<sup>22</sup> In the early stages, basal cortisol secretion is maintained, although secretion in response to stress is impaired and, depending on the situation any stress, such as infection and trauma, can precipitate an acute adrenal crisis. With progressive disease, basal cortisol secretion is affected, leading to the insidious onset of symptoms of the disease. Several other organ-specific autoimmune diseases (eg, thyroid disorders, type 1 diabetes mellitus (DM), vitiligo, hypoparathyroidism, vitamin B<sub>12</sub> deficiency and premature ovarian insufficiency) frequently occur in combination with PAI,<sup>23</sup> or as part of APS-1 and APS-2.<sup>14</sup>



**Figure 2** Types of AI. ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CRH, corticotropin-releasing hormone; DHEAS, dehydroepiandrosterone sulfate.

Patients with APS-1, which is a rare autosomal recessive disease caused by a mutation in the autoimmune regulator (AIRE) gene, will have at least two of three main components: PAI, hypoparathyroidism and chronic mucocutaneous candidiasis, and those with APS-2, a far more common condition than APS one and with polygenic inheritance, have at least two of the three endocrinopathies, namely, PAI, type 1 diabetes and autoimmune thyroiditis. Both these syndromes can present at any stage of life with new components appearing throughout life. Patients will have circulating autoantibodies and suffer from endocrine failure due to lymphocytic infiltration of the affected glands.<sup>24</sup>

Another rare congenital disorder of PAI, caused by DAX1 mutations, is X-linked adrenal hypoplasia congenita in which affected men present with early-onset PAI and develop hypogonadotropic hypogonadism and azoospermia during puberty.<sup>25</sup> Adrenoleukodystrophy (ALD), an X-linked recessive condition, occurs due to a ABCD1 gene mutation and affects 1 in 20 000 men with PAI and is due to defective  $\beta$ -oxidation of very long-chain fatty acids (VLCFAs). These patients often develop neurological symptoms many years later.<sup>26</sup> Triple A (Allgrove) syndrome, an autosomal recessive condition, characterised by features of achalasia, alacrima and PAI, is another rare cause of AI.<sup>27</sup>

In the early stages in SAI and TAI, basal ACTH secretion is maintained, while stress-induced ACTH secretion is affected. With time, basal ACTH secretion is also affected causing gradual atrophy of zonae fasciculata and reticularis of the adrenal cortex but aldosterone secretion by the zona glomerulosa remains intact.<sup>22</sup>

In practice, it can often be difficult to distinguish between SAI and TAI, and many patients may have elements of both hypothalamic and pituitary defects. If SAI is diagnosed, the insulin tolerance test or CRH stimulation test can be used to distinguish between a hypothalamic (tertiary) and pituitary (secondary) cause, although it is rarely used in clinical practice.<sup>28</sup> The distinction is not clinically relevant, although diabetes insipidus is more likely to occur in TAI caused by hypothalamic damage.

## CLINICAL MANIFESTATIONS OF AI

The symptoms of PAI (table 2) are usually of insidious onset and, except for salt craving, are non-specific.<sup>24</sup> As a result, the diagnosis is often delayed or missed altogether,<sup>29</sup> with some patients presenting in the emergency department with an acute life-threatening adrenal crisis.<sup>30</sup>

Many patients with PAI have signs and symptoms of associated diseases which are seen in as many as 50% of patients

with Addison disease.<sup>23</sup> The presence of hypoparathyroidism or *Candida* infections should always prompt investigation for APS-1.<sup>24</sup>

SAI is usually milder than PAI as aldosterone secretion remains intact (figure 2). Due to normal or low ACTH and preserved aldosterone level, hyperpigmentation, dehydration and hyperkalaemia are not seen in these patients. However, deficiencies of other pituitary hormones can influence or may be the dominant part of the clinical picture.

Hyponatraemia can occur in both PAI and SAI, although underlying aetiology is different in each case. In PAI, hyponatraemia (and hypovolaemia) is caused by aldosterone deficiency, whereas in SAI, hyponatraemia is due to inappropriate vasopressin secretion (and water retention) due to the lack of cortisol, which leads to dilutional or hypervolaemic hyponatraemia.<sup>31</sup>

TAI, usually due to exogenous steroid treatment, is a heterogeneous group of conditions, and these patients may have Cushingoid features despite having suppressed HPA axis.

## DIAGNOSIS OF AI

It is important to constantly look out for AI in patients presenting with non-specific symptoms. Once suspected, it is usually easy to confirm or refute the clinical suspicion by performing some simple tests.

A morning sample for serum cortisol, taken between 07:00 and 08:00, is usually the first test performed in patients with suspected AI, and concentration of <80 nmol/L is strongly suggestive of AI,<sup>32</sup> while a level of  $\geq 365$  nmol/L was able to predict normal adrenal function with 100% sensitivity.<sup>33</sup> However, concentrations below 354 nmol/L should prompt a short synacthen test (SST).<sup>34</sup>

Basal plasma ACTH is used to differentiate between PAI and SAI/TAI with high ACTH (double the upper reference limit) suggestive of PAI. Many patients with PAI will also have low aldosterone and high plasma renin activity (PRA), and some may have low dehydroepiandrosterone sulfate (DHEAS) concentrations (figures 1 and 2).

The SST remains the most widely used test to diagnose AI and involves intramuscular or intravenous administration (both routes generate equivalent results<sup>35</sup>) of 250  $\mu$ g synacthen (cosyntropin, synthetic ACTH) and collection of blood samples at 0, 30 and 60 min. The test may be performed at any time throughout the day as effects of the circadian rhythm are neutralised due to very large dose of ACTH being administered and poststimulation value being used for diagnostic purposes. However, we have previously shown that 30 min sample does not add any additional diagnostic utility and can be omitted thus simplifying SST even further and saving on cost and resources.<sup>36</sup> However, it is the the 30 min sample that has been shown to have best correlation with the Insulin Tolerance Test (ITT),<sup>37</sup> and many centres across the UK have chosen to retain it.<sup>38</sup> The guidelines currently do not distinguish between these different time points when recommending a peak cut-off value to exclude AI.

There are a number of assays now available to measure serum cortisol, and it is now well established that differences in the assays do have a major impact on the interpretation of cortisol values in SST. A peak cortisol level of 500 nmol/L at 30 or 60 min after ACTH administration is traditionally considered as sufficient evidence for normal adrenal function,<sup>39</sup> although the cut-off for a normal cortisol response to synacthen may range from 420 to 574 nmol/L depending on assay used.<sup>40</sup>

Due to much lower cross reactivity with other endogenous steroids, newer monoclonal immunoassays such as Elecsys

**Table 2** Clinical manifestations of primary adrenal insufficiency

Symptoms	Signs	Laboratory findings
<ul style="list-style-type: none"> <li>▶ Fatigue and lethargy.</li> <li>▶ Weight loss.</li> <li>▶ Salt craving.</li> <li>▶ Postural dizziness.</li> <li>▶ Anorexia.</li> <li>▶ Abdominal discomfort.</li> <li>▶ Joint and muscle aches.</li> <li>▶ Loss of axillary and pubic hair in women due to loss of adrenal androgens.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Increased pigmentation of the skin and mucous membranes, especially on sun-exposed areas and those subject to friction, such as knuckles, skin creases, elbows, scars, breast areola (caused by stimulation of dermal melanocortin receptors due to high ACTH and other pro-opiomelanocortin peptides).</li> <li>▶ Low blood pressure.</li> <li>▶ Orthostatic hypotension.</li> <li>▶ Failure to thrive in children.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Hyponatraemia.</li> <li>▶ Hyperkalaemia.</li> <li>▶ Hypoglycaemia.</li> <li>▶ Hypercalcaemia.</li> <li>▶ Normochromic anaemia, eosinophilia and lymphocytosis.</li> </ul>

ACTH, adrenocorticotropic hormone.



Cortisol generation II (Roche Diagnostics, Indianapolis, Indiana) and Beckman Access Cortisol (Beckman Coulter, City, California) consistently produce cortisol values that are 20%–30% lower than those with older polyclonal antibody assays, with 30 min cortisol level being 374<sup>41</sup> and 403 nmol/L<sup>42</sup> in two studies. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is a non-antibody, structural assay which is highly specific for cortisol. In a recently published study, new cortisol cut-off using LC-MS/MS were 412 and 485 nmol/L at 30 and 60 min, respectively.<sup>43</sup> It is therefore important *not* to use a historically accepted cut-off of 500 nmol/L in SST for the newer, more specific cortisol assays to avoid false-positive results for AI.

In patients with mild or recent onset SAI or TAI, the SST may be normal because of the very large dose of ACTH that is given (leading to ACTH concentrations more than a thousand times of the normal physiological peak<sup>44</sup>) and because it takes couple of weeks for the adrenal cortex to lose its sensitivity to ACTH stimulation. As such, the low-dose ACTH stimulation test using 1 µg of cosyntropin, which provides more physiological plasma ACTH concentration, has been advocated to detect mild SAI,<sup>45</sup> but it is now believed that high-dose and low-dose SSTs yield identical results because the concentrations of plasma ACTH postinjection greatly exceed the maximum endogenous physiological stimulus to the adrenal cortex even in low dose test.<sup>44 46</sup>

It is important to bear in mind that most tests use serum *total* cortisol and therefore abnormalities of cortisol-binding globulin (CBG), for example, pregnancy, oral oestrogen treatment, cirrhosis and nephrotic syndrome, will affect the results.<sup>47</sup> Plasma cortisol is 90% protein bound (80% bound to CBG and about 10% to albumin) and has to be dissociated from binding proteins using an agent which may vary from one manufacturer to another.<sup>48</sup> Cortisol results with some methods are also influenced by albumin concentration of specimens, which may affect the accuracy of result.<sup>49</sup>

Salivary cortisol is commonly used in the diagnostic work-up of hypercortisolism.<sup>50</sup> There has been some interest in its use in the diagnosis of AI due to ease of sample collection, and free concentration of the hormone is measured, thus avoiding the interference due to changes in concentrations of binding globulins.<sup>51</sup>

The diagnosis of PAI in pregnant women is particularly challenging due to overlapping symptoms and the fact that pregnancy is a state of 'physiological' hypercortisolism.<sup>52</sup> The circulating cortisol levels are twofold to threefold higher in pregnancy at term time than those in non-pregnant women, partly due to estrogen-induced tripling of CBG levels.<sup>53</sup> This produces diagnostic challenge as applying cut-off threshold based on norms determined in non-pregnant populations will be misleading. It has been proposed that salivary cortisol should be used as the preferred measurement of assessing adrenal reserve and responsiveness to ACTH in pregnancy, although the cut-off values remain a matter of some debate.<sup>54</sup>

ITT is considered the gold standard to test the entire HPA axis by inducing hypoglycaemia (plasma glucose <2.2 mmol/L) following the intravenous administration of insulin (0.1–0.15 unit/kg), which should trigger a rise in serum cortisol.<sup>55</sup> It is particularly useful for the detection of early SAI.

The single-dose overnight metyrapone stimulation test has often been advocated in patients when ITT cannot be used. The administration of metyrapone results in decreased cortisol levels through inhibition of 11-β-hydroxylase (thus inhibiting the conversion of 11-deoxycortisol to cortisol), which in turn leads to accumulation of the substrate 11-deoxycortisol via ACTH stimulation.<sup>56</sup> This test does not induce hypoglycaemia and is

often performed on an outpatient basis. There is a potential risk of precipitating an acute adrenal crisis during this test in patients with undiagnosed AI insufficiency, and it is important to ensure that the patient has an adequate cortisol reserve (eg, 09:00 cortisol >200 nmol/L) prior to performing the test. However, this test is now rarely used due to limited availability of metyrapone and wide variations in the measurement of 11-deoxycortisol in blood and urine. Moreover, synthetic ACTH and cortisol assays are now readily available, making SST as the favoured test for the diagnosis of AI.

The use of ITT should be considered when the results of the SST are equivocal (eg, a positive test in the context of a low clinical suspicion or a negative test in the context of high clinical suspicion).

Once confirmed, it is important to try to establish the cause of AI. In acquired PAI, 21-hydroxylase autoantibodies should be checked to confirm the diagnosis of autoimmune PAI.<sup>57</sup> These patients should also be tested for associated autoimmune conditions (including thyroid disease, DM, premature ovarian failure, coeliac disease, autoimmune gastritis and vitamin B<sub>12</sub> deficiency) at the time of diagnosis and annually thereafter.<sup>39</sup>

If 21-hydroxylase autoantibodies are absent, CT scan of adrenal glands should be considered to help diagnose structural causes of PAI such as infections, tumours and bleeding. In younger patients (<20 years), APS-1 should always be considered, and all male patients should have VLCFA tested in their serum and, if found raised, should have molecular genetic testing to confirm the diagnosis of ALD.

In patients suspected with SAI, other pituitary hormones should be assayed, and an MRI of pituitary should be organised to look for structural causes (eg, tumour, infiltrative processes such as lymphocytic hypophysitis or granulomatous infiltration).<sup>58</sup> Isolated ACTH deficiency is a diagnosis of exclusion.

In TAI, a detailed drug history is vital, including use of inhaled, injected and topical steroids. Importantly, opiates are the second most common drugs to cause TAI, and history of recreational opioid use may not always be easy to obtain.

Immune checkpoint inhibitors (ICIs) such as nivolumab, pembrolizumab and ipilimumab are monoclonal antibodies and are now used widely in the management of various cancers. Their toxicities are autoimmune in nature (immune-related adverse events) and can affect endocrine glands, including pituitary (hypophysitis causing SAI) and adrenal glands (causing PAI).<sup>59</sup>

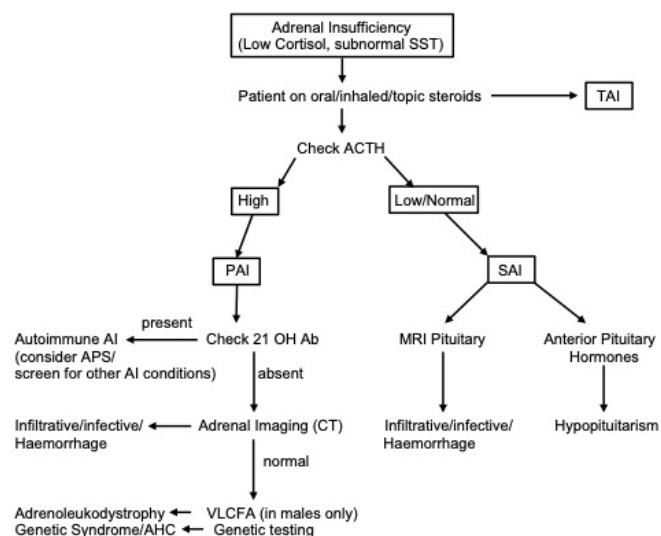
An algorithm for the diagnostic approach of AI is depicted in figure 3.

## MANAGEMENT OF AI

Patients with PAI require steroid replacement for life, and those with SAI and TAI will require steroids long term, if not for life. Patients with TAI secondary to long-term steroid therapy should stop treatment gradually to prime adrenal glands and allow them time to recover their functions. Adrenal reserve can be tested by SST after the patient has been on a small dose of steroid (eg, prednisolone 5 mg, hydrocortisone 20 mg or cortisone acetate 25 mg) for at least 1–4 weeks. Patients on steroids with long half-life (eg, dexamethasone) should be switched to hydrocortisone before performing SST, and the test should be performed at least 24 hours after the last dose of exogenous steroid.

Treatment for ICI-induced AI involves steroid replacement with patients continuing ICI. Importantly, AI can even occur several months after discontinuing an ICI.<sup>60</sup>

All patients on steroids should carry a steroid card and wear a MedicAlert bracelet to inform medical personnel on their steroid



**Figure 3** Algorithm for the diagnostic approach to the patient with AI. ACTH, adrenocorticotropic hormone; Adhydrocortisone, adrenal hypoplasia congenita; AI, adrenal insufficiency; APS, autoimmune polyendocrinopathy syndrome; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; SST, short synacthen test; TAI, tertiary adrenal insufficiency; VLCFA, very long-chain fatty acid.

dependence status because any delay in the administration of hydrocortisone in an emergency can have serious consequences.<sup>61</sup>

### Glucocorticoid replacement

In healthy individual, adrenal glands produce 5–10 mg of cortisol/ sq. m body surface area/day in a circadian manner, with a peak in the morning and a nadir at midnight.<sup>62</sup> This is equivalent to a daily oral replacement dose of 15–25 mg hydrocortisone for an adult.

The standard choice of glucocorticoid replacement in AI is oral hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg/day), with hydrocortisone being the preferred medication in most countries. Cortisone acetate needs to be activated to hydrocortisone by hepatic 11 $\beta$ -hydroxysteroid dehydrogenase type 1, which leads to a slightly delayed onset of action.

Hydrocortisone is usually given two or three times a day with the first (and largest) dose, which should not exceed 10 mg, as soon as the patient is awake, and the last dose about 6 hours before bedtime to avoid sleep disturbances. Such a dosing regimen, however, remains imperfect and fails to mimic the physiological cortisol circadian rhythm<sup>63</sup> and inevitably results in temporary over-replacement or under-replacement.

Modified-release hydrocortisone once per day (15–25 mg) is now available and seems to provide a more circadian-based serum cortisol profile<sup>63</sup> with favourable metabolic effects on weight, blood pressure, and glucose metabolism, and improved health-related quality of life.<sup>64</sup>

In some countries, prednisolone, given in doses of 3–5 mg/day, remains the only treatment option for AI despite concerns about more frequent dyslipidaemia<sup>65</sup> and reduced bone mineral content<sup>66</sup> compared with hydrocortisone. It is cost effective and can be administered once per day dose, thus improving compliance. In the Endocrine Society Clinical Practice guidelines (2016), prednisolone, given once or two times per day, is suggested as an alternative to hydrocortisone, particularly in patients with reduced compliance.<sup>39</sup>

Dexamethasone should not be used to treat AI due to its long half-life, which leads to Cushingoid side effects. Subcutaneous pump treatment is an option, and the only effective way of reconstituting the circadian variation in cortisol.<sup>67</sup>

In a recently published study compiling data from 2648 patients with AI (almost equal number of patients with PAI and SAI) across the UK, 72% of patients were noted to be on hydrocortisone, 26% on prednisolone and 2% modified release hydrocortisone.<sup>68</sup>

One of the main challenges in the management of AI is to assess the adequacy of glucocorticoid replacement. In the absence of an established biomarker of cortisol activity, some clinicians rely on clinical symptoms and others use cortisol day curve<sup>69</sup> based on serum samples, saliva or blood spots from capillary finger-prick samples. It is not yet established if such monitoring improves outcomes in these patients.

### Mineralocorticoid replacement

Patients with SAI and TAI do not need mineralocorticoid replacement. Aldosterone deficiency in PAI should be treated with fludrocortisone (0.05–0.20 mg), in a morning dose of once per day, with higher doses given to physically active people. Because of the long half-life of fludrocortisone, divided doses are not required. Patients should be advised not to restrict their salt intake.

Mineralocorticoid replacement is evaluated clinically by measuring blood pressure and by asking for symptoms such as persistent salt cravings, postural giddiness, and leg swelling and biochemically by checking electrolytes. Some clinicians measure plasma renin activity (PRA) with the aim to keep it towards the upper reference range.<sup>70</sup> However, interpretation of PRA is dependent on the time of day, body position and medication intake and is no longer advisable.

The aim of mineralocorticoid replacement is to normalise blood pressure and potassium, and inadequate substitution may be responsible for poor cardiometabolic outcome and impaired sense of well-being.<sup>71</sup>

### Adrenal androgen replacement

Patients with PAI often have adrenal androgen deficiency, and a 6-month trial of DHEA, 25–50 mg once per day is suggested in patients with PAI who continue to experience low energy levels, poor well-being and (in women) poor libido despite optimal glucocorticoid and mineralocorticoid replacement.<sup>72</sup> Dose of DHEA should be adjusted by aiming to normalise morning serum DHEAS levels.

### TREATMENT OF ADRENAL CRISIS

An acute adrenal crisis is a life-threatening emergency that requires immediate treatment even if blood tests cannot be carried out or results are not yet available. Patient will often present with accentuation of their chronic non-specific symptoms with dehydration leading to hypotension and shock. Dehydration can be severe and perpetuated if life-threatening hypercalcaemia is associated with Addisonian crisis.<sup>73</sup> Blood tests will usually reveal low sodium, high potassium, low glucose and a biochemical picture consistent with acute kidney injury.<sup>74</sup>

Treatment of an acute adrenal crisis is summarised in [table 3](#).

### DOSE ADJUSTMENTS AND SICK DAY RULES

Patients with AI should adjust their glucocorticoid dose when exposed to stressful situations and while undergoing a medical or surgical procedure according to the degree of stress induced.

**Table 3** Treatment of an acute adrenal crisis

Hydrocortisone	<ul style="list-style-type: none"> <li>▶ 100 mg intravenous bolus stat followed by 50–100 mg intravenous or intramuscular four times a day continued for 24–48 hours until the patient can take oral medication (alternative 200 mg/24 hours by continuous intravenous infusion).</li> <li>▶ Fludrocortisone should be restarted when the hydrocortisone dose falls to &lt;50 mg/day.</li> <li>▶ Dehydroepiandrosterone replacement is not required.</li> <li>▶ Monitor renal profile at least every 12 hours and continue regular monitoring until electrolyte imbalance and acute kidney injury are corrected.</li> </ul>
Intravenous fluids	<ul style="list-style-type: none"> <li>▶ 1 L normal saline intravenous infusion over an hour followed by repeated infusion at a slower rate (usually 4–6 L in 24 hours).</li> <li>▶ Frequent haemodynamic monitoring and measurement of serum electrolytes to avoid fluid overload.</li> </ul>
Other treatment	<ul style="list-style-type: none"> <li>▶ Admission to the high-dependency unit.</li> <li>▶ Prophylaxis of gastric stress ulcer and low-dose heparin.</li> <li>▶ Antibiotic treatment.</li> </ul>
To prevent future adrenal crises	<ul style="list-style-type: none"> <li>▶ Explore the medical and behavioural causes precipitating adrenal crisis, (eg, compliance issues).</li> <li>▶ Patient education.</li> <li>▶ Annual influenza immunisation (and pneumococcal vaccination when older than 60 years).</li> <li>▶ Emergency hydrocortisone injection (every patient should be issued with an emergency injection kit and advised of training for patients and carers/families on their use).</li> <li>▶ Sick day rules guidance.</li> <li>▶ Advise to register with local ambulance service as 'steroid dependent'.</li> <li>▶ Steroid card/medic bracelet.</li> </ul>

However, the optimal dose, frequency and duration of enhanced coverage remain contentious.

In case of vomiting, diarrhoea or when the patient is fasting (eg, prior to an elective surgical procedure), glucocorticoids should be administered parenterally, preferably intravenously. The current evidence supports the use of hydrocortisone doses not exceeding 200 mg/day.<sup>75</sup> Following an uncomplicated surgical procedure, glucocorticoid dose can usually be reduced to baseline after about 3 days.<sup>76</sup>

In case of medical illness, it is generally suggested that patients should double or triple their daily dose of glucocorticoid therapy during a febrile illness until recovery.<sup>77</sup>

### AI AND COVID-19

Patients with AI have a slightly increased overall risk of infections, including coronavirus; they are at an increased risk of complications due to the potential for an adrenal crisis to be triggered by the infection. It is suggested that patients with AI and suspected (or confirmed) COVID-19 infection should increase their hydrocortisone dose to 20 mg four times per day, and those on modified release hydrocortisone should switch to the regular, immediate release preparation at a dose of 20 mg orally every 6 hours. Patients on prednisolone 5–15 mg/day should take 10 mg every 12 hours and those on prednisolone >15 mg should split their usual daily dose into two equal doses 12 hours apart.<sup>78</sup>

Patients should be advised to take fludrocortisone at their usual daily dose.

If the patient becomes ill, usual sick day rules apply and patient should be advised to call the ambulance if they have continuous high temperature, shortness of breath or diarrhoea and vomiting.

In a recent study of histopathological examination of adrenal tissue obtained from the autopsies of 40 patients who died from COVID-19, evidence of cellular damage and small vessel vasculitis was found, suggesting that the adrenal gland is a prominent target for the viral infection.<sup>79</sup> Further studies are required to establish whether adrenal involvement in COVID-19 is likely to lead to AI<sup>80</sup> or perhaps symptoms of long COVID-19.

### OUTLOOK FOR THE FUTURE

There continue to remain significant challenges in the diagnosis and management of AI. Patients with Addison's disease require lifelong glucocorticoid and mineralocorticoid therapy on a daily basis, and despite many advances over the last few decades, it has not been possible to mimic the physiological rhythm of cortisol, which adds to the risk of increased morbidity and mortality in these patients.

Many patients continue to present with adrenal crisis as the first manifestation of AI due to delay in diagnosis, and it is important that doctors and nurses are educated to enable them to suspect and diagnose the condition in a timely manner.

A number of options are currently being explored to halt and possibly reverse the autoimmune destruction of the adrenal cortex, including B lymphocyte-depleting immunotherapy with rituximab,<sup>80</sup> regular subcutaneous tetracosactide (ACTH1-24)<sup>81</sup> therapy,<sup>82</sup> dual therapy with rituximab and repeated depot tetracosactide.<sup>83</sup>

Transplantation of adrenocortical tissue is another promising approach, and a successful mother-to-daughter allograft has been reported in a young patient with AI secondary to severe sepsis.<sup>84</sup> Allografts of whole adrenal–kidney–pancreas have also been described in a patient with type 1 diabetes and concomitant autoimmune AI with satisfactory outcome at 1 year.<sup>85</sup> Stem cells provide the potential to regenerate the adrenocortical tissue in patients with AI, and this is currently an area of intense research.<sup>86</sup>

### CONCLUSION

Timely identification of AI is critical as it can become a life-threatening condition in a stressful situation due to impaired cortisol response. Despite the challenges of mimicking the physiological rhythm, glucocorticoid replacement therapy is life-saving and leads to dramatic improvement in overall outcome. It is important to educate the patient and family members about the need to wear a medical alert bracelet or necklace and to carry a steroid card.

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