ADDISON'S DISEASE

The focus for this edition is Addison's disease, for which Prescribed Minimum Benefits are applicable. Detail of the legislated algorithm for Addison's disease can be found on the following website: **www.medicalschemes.com**. The article below provides a broad overview only, and not a detailed approach to treatment.

Addison's is a rare endocrine disorder, usually caused by destruction of the adrenal cortex causing deficiencies in the body's levels of cortisol and aldosterone. It is also called primary adrenocortical insufficiency (ICD 10 code E27.1), chronic primary adrenal insufficiency or hypocorticalism.

Secondary Addison's disease, due to pituitary disease, is characterised by insufficient cortisol without changes in aldosterone.

Addison's has an occurrence rate of 1:100 000, affecting the sexes equally and occurring at any age. It is associated with autoimmune endocrinopathies, e.g. thyroid disorders or diabetes mellitus type 1.

Addison's is easily diagnosed and treated, but is potentially lethal if unrecognised. Patients usually have few symptoms unless they are severely stressed.

AETIOLOGY

At the time when the disease was first described the most common cause of Addison's was tuberculosis (TB), until treatment for TB was developed. TB is, however, still one of the major causes of Addison's in South Africa. The main cause in Western countries is now autoimmune disorders, which contributes to 70 - 90% of cases.

Infectious causes of Addison's disease include *Mycobacterium* and other bacteria, viral and fungal infections.

Drugs inhibiting cortisol biosynthesis affect only patients with limited pituitary/adrenal reserve and not patients with normal hypothalamic-pituitary-adrenal functioning.

Drugs which accelerate cortisol metabolism can precipitate an Addisonian crisis owing to their mechanism of action.

Cancers which could lead to Addison's by metastatic infiltration of the adrenal glands include those of the lung, breast, stomach or colon. However, Addison's is rare, as most of the adrenal cortex must be destroyed before hypofunction is evident.

Pituitary disease, e.g. tumours, infections, infarction, can cause secondary adrenal insufficiency and usually results in panhypopituitarism. Isolated adrenocorticotrophic hormone (ACTH) deficiency is rare and is usually caused by an autoimmune process.

Prolonged use of high-dose synthetic glucocorticoids may result in ACTH deficiency and consequent adrenal insufficiency. This is the most common cause of tertiary adrenal insufficiency.

CLINICAL MANIFESTATIONS

Hyperpigmentation is the most characteristic manifestation of chronic primary adrenal insufficiency. It occurs in nearly all patients with primary adrenal insufficiency.

Chronic primary adrenal insufficiency

General clinical symptoms include fatigue, generalised weakness, lassitude, chronic malaise, and anorexia and weight loss. Gastric complaints, hypotension, hypoglycaemia, sexual dysfunction and electrolyte disturbances also occur.

Primary adrenal insufficiency in children

- Weight loss is not as prominent as in adults.
- Affected children are short — usually between the 3rd and 25th percentile of their age group.
- They suffer from candidiasis of the mouth.
- They have hypocalcemia due to hypoparathyroidism.

Primary adrenal insufficiency in patients with HIV/AIDS

- The incidence of Addison's among this patient group is up to 20%.
- Fatigue is the most common symptom.
- Thirty-three per cent of patients suffer from hyperpigmentation.
- Fifty per cent of patients have hyponatraemia.

Addisonian crisis

An Addisonian crisis is a clinical emergency. It is usually triggered by a sudden increase in stress, a severe infection or a bilateral infarction or haemorrhage of the adrenal gland.

Symptoms include anorexia, nausea and vomiting, abdominal pain, weakness, lethargy, confusion and eventually coma.

DIAGNOSIS

A clinical diagnosis is often difficult because early disease symptoms are nonspecific. Although hyperpigmentation of the skin and gums is the most characteristic manifestation, it

is not always present and can in other instances also be the result of drugs such as antineoplastics, antimalarials, tetracyclines, phenothiazines and zidovudine.

Laboratory testing consists of three stages and is necessary to determine the type of adrenal insufficiency. This will demonstrate inappropriately low cortisol levels and whether or not the deficiency is ACTH dependent.

Interpretation of serum cortisol levels:
- < 275 nmol/l (< 10 µg/dl) suggests the possibility of a positive diagnosis
- < 80 nmol/l (< 3 µg/dl) confirms adrenal insufficiency as diagnosis.

Salivary cortisol levels at 08h00:
- >16 nmol/l (> 5.8 ng/ml) excludes the diagnosis of adrenal insufficiency
- < 5 nmol/l (< 1.8 ng/ml) indicates a high probability of the diagnosis of adrenal insufficiency.

The ACTH stimulation test is used to determine adrenal insufficiency and to assess whether it is primary or secondary. The low-dose ACTH test is performed by measuring serum cortisol immediately before and 30 minutes after intravenous injection of a low dose of cosyntropin. Little or no respone indicates primary adrenal insufficiency.

TREATMENT

Patient education

Both the patient and his/her close family should be instructed on:
- the nature of the hormonal deficiency
- the rationale for replacement therapy
- the use of the maintenance medication
- the changes required during minor illness
- when to consult a physician
- when/how to administer dexamethasone IM in an emergency.

Changes required during minor illness are explained as the 3 x 3 rule stipulating that during minor illnesses, such as upper respiratory tract infection, the glucocorticoid dose can be increased by 3 times the daily dose for 3 days by the patient without consulting the doctor. This will reduce the fever and malaise without compromising the immune response. However, the patient must consult the doctor if the illness worsens and s/he cannot go back to the standard glucocorticoid dose on day 4.

Emergency precautions

The risk to the patient in an emergency situation is the lack of:
- serum cortisol to respond to induced stress
- a normal renin-angiotensin-aldosterone response to hypovolaemia.

Patients should always:
- Wear/carry a disease identification card or bracelet/necklace detailing the following:
  - information on the condition
  - daily medication and dose taken
  - doctor contact details.
- Have in possession a 1 ml dexamethasone pre-filled syringe for emergency IM injection. An emergency constitutes any of the following situations:
  - substantial blood loss (i.e. > 250 ml)
  - fracture/neurogenic shock
  - nausea/vomiting and inability to take and keep down oral medication
  - symptoms of acute adrenal insufficiency
  - finding an unresponsive patient.

The patient/person assisting should obtain medical attention as quickly as possible after administration of the injection.

Chronic treatment (Table I)

Treatment of primary Addison's involves replacing the lack of cortisol and aldosterone with similar steroids. Cortisol is usually replaced by oral cortisone acetate or hydrocortisone or prednisone in divided doses. Aldosterone is replaced with fludrocortisone (Florinef) tablets. The mineralocorticoid fludrocortisone prevents:
- sodium loss
- intravascular volume depletion
- hyperkalaemia.

Fludrocortisone is given in combination with hydrocortisone (10 - 30 mg/d) or cortisone (10 - 37.5 mg/d) because of only moderate glucocorticoid activity.

Cortisone is not biologically active and must undergo hepatic metabolism to cortisol. The oral administration of cortisone/hydrocortisone does not mimic the normal daily rhythm of cortisol secretion. It is absorbed within 30 minutes of ingestion. A longer acting preparation is therefore usually preferable. It should however be noted that a patient already on a short-acting preparation should not be changed to a longer acting preparation.

Cortisol levels are at their highest between 04h00 and 08h00, and the ideal time to administer a dose of cortisone would be between 03h00 and 04h00, when the circadian ACTH secretion begins to increase. Since slow-release preparations are not available, patients should be instructed to take their medication at bedtime. The plasma ACTH levels are thus lowered to the normal range and provide adequate circulating glucocorticoids when the patient awakens.

In cases of emergency or where a patient undergoes surgery, IV hydrocortisone is administered.

A patient's therapy is adjusted according to his/her weight, age and co-existing medical conditions. Obese patients usu-

ally have higher doses due to the more rapid metabolism of the steroids, whereas children or small adults have a lower metabolism of the steroids.

Dosage of the steroids also requires adjustment if used in combination with drugs which induce accelerated hepatic metabolism, such as phenytoin, barbiturates, rifampicin and others.

The mineralocorticoid dose may have to be increased in summer owing to increased salt loss through perspiration. Salt intake should be increased liberally, especially with exercise.

It is critical that the underlying disease and cause of the adrenal insufficiency is treated where possible, e.g.
- treatment of TB and histoplasmosis with antibiotics
- correction of causes of adrenal infarct.

Treatment of the Addisonian crisis

The initial goal is treatment of hypotension and reversal of the electrolyte imbalances and cortisol deficiency. This involves fluid, salt and cortisol replacement:
- 2 – 3 l of 0.9% saline solution or 5% dextrose in 0.9% saline solution
- Dexamethasone sodium phosphate 4 mg or hydrocortisone sodium succinate 100 mg 6 – 8 hourly
- Treat the underlying cause of the crisis, e.g. infection.

Mineralocorticoid replacement therapy need not start immediately since the sodium-retaining effect takes a few days. In patients without severe complications, the IV therapy can be tapered to oral therapy over 1 - 3 days.

Pregnancy in primary adrenal insufficiency

The use of glucocorticoid and mineralocorticoid replacement doses is continued, but pregnant women may occasionally require increased doses in the third trimester. During the first trimester of pregnancy it may be necessary to administer medication IM if nausea and vomiting prevent absorption of oral medication.

CONCLUSION

Before the introduction of glucocorticoids, the expected lifespan of patients suffering from Addison's disease was approximately 2 years from diagnosis. Glucocorticoids have, however, made it possible for all patients suffering from Addison's disease to lead a normal productive life, including vigorous exercise. There are no physical or occupational restrictions and patients have a normal life expectancy. Even children with adrenal insufficiency experience normal linear growth and pubertal development when treated adequately (i.e. not over-treated). The prognosis of the patient with other causes of adrenal insufficiency depends on the underlying cause.

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Table I. **Drugs used for chronic treatment of primary Addison's disease**

Drug	Dose	Replacement for
Cortisone acetate, e.g. Cortogen	25 mg/d in divided doses	Cortisol
Hydrocortisone	20 mg/d in divided doses	
Prednisone, e.g. Panafcort Meticorten	5 mg once daily	
Dexamethasone, e.g. Decadron Decasone (IV)	0.5 mg once daily	
Fludrocortisone acetate, e.g. Florinef	0.1 mg 3 x per week to 0.2 mg /d	Aldosterone