CHAPTER 8

ENDOCRINE DISORDERS

8.1 ACROMEGALY

E22.0

DESCRIPTION

Acromegaly is a disorder caused by growth hormone (GH) hypersecretion usually due to a pituitary adenoma, with associated morbidities, and increased mortality.
This condition should be managed at a tertiary centre.
Transsphenoidal adenomectomy is the accepted form of primary therapy.
Radiotherapy post operatively may be required. In addition, adjunctive medical therapy may be required in specific circumstances.

Investigations

If the diagnosis is suspected, screening should be done in consultation with a specialist.

REFERRAL

All patients with suspected acromegaly to a hospital with endocrine and neurosurgery facilities.

8.2 ADRENAL INSUFFICIENCY (ADDISON DISEASE)

E27.1/E27.2

DESCRIPTION

Primary adrenocortical insufficiency.

Clinical presentation

Acute crisis: (not all symptoms and signs may occur in a particular patient, so a high index of suspicion is needed).

- » hypotension
- » fever
- » GIT disturbances
- » dehydration
- » weakness
- » depressed mentation
- » hypoglycaemia
- » hyponatraemia
- » hyperkalaemia
- » acidosis

Chronic:

- » hyperpigmentation
- » weakness and fatigue
- » loss of weight
- » postural dizziness
- » arthralgia
- » GIT disturbances
- » hypotension
- » hypoglycaemia
- » hyponatraemia
- » hyperkalaemia

Always consider this diagnosis in a thin, hypotensive, hypoglycaemic patient, or during stress e.g. sepsis. **The combination of hyponatraemia and hyperkalaemia should suggest possible primary adrenal insufficiency.**
Note: Treatment of suspected acute adrenal failure should never be delayed to obtain results of diagnostic procedures.

Investigations

08h00 serum cortisol level (or at time of presentation in acute crisis):

- >500 nmol/L: virtually excludes the diagnosis
- with newer assays cortisol concentrations >450 nmol/L are acceptable to exclude hypoadrenalism
- 100–450 nmol/L is indeterminate and may require an adrenocorticotropic hormone (ACTH) stimulation test:

- ACTH depot, IM, 1 mg with blood sampling at 60 minutes.
  - Post ACTH, serum cortisol level normal value: >550 nmol/L or double the pre-test level.

LoE:III[i]

GENERAL MEASURES

All patients with confirmed hypoadrenalism.
Investigate for other causes such as sepsis and treat accordingly.

MEDICINE TREATMENT

Acute crisis

E27.2

Before administering hydrocortisone, ensure blood samples are taken for serum cortisol and plasma ACTH, if feasible.

- Hydrocortisone, IV, 100 mg 6 hourly.
  - Change to oral maintenance therapy once stable. *LoE:III[ii]*

To maintain adequate intravascular volume guided by blood pressure:

- Sodium chloride 0.9%, IV with regular glucose monitoring, and 50% dextrose boluses if required.
  - Beware of fluid overload if the combination of sodium chloride 0.9%/dextrose 5% is utilised.
  - The fluid deficit is often several litres. *LoE:III[iii]*

Monitor glucose levels closely and treat hypoglycaemia if present.
Note: All suspected cases should be referred for full evaluation, prior to chronic maintenance therapy.

Chronic

As maintenance therapy:

- Hydrocortisone, oral.
  - Start with 10 mg in the morning and 5 mg at night.

- Increase the dose according to clinical response up to 20 mg in the morning and 10 mg at night.
- In patients requiring a midday dose, a suggested regimen is 10 mg in the morning, 5 mg at midday and 5 mg in the early evening.

OR *LoE:III*

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral.
  - Start with 5 mg daily.
  - Increase to maximum of 7.5 mg daily, if necessary. *LoE:III[iv]*

For patients who have symptoms of mineralocorticoid deficiency:

- Fludrocortisone, oral, 50–100 mcg daily may be required to normalise the potassium and to reduce postural hypotension in primary hypoadrenalism.
  - Titrate dose of fludrocortisone in consultation with a specialist.

LoE:III[v]

Monitor response to therapy with:
» Symptoms: improvement in fatigue and GIT disturbances.
» Blood pressure: normotensive and no postural drop.
» Electrolytes: normal Na+ and K+.

During times of severe "stress" i.e. acute illness, surgery, trauma, etc.:

- Hydrocortisone, IV, 100 mg 6 hourly. *LoE:III[vi]*

Minor stressors e.g.: Influenza, diarrhoeal illness, chest infections and dental procedures warrant doubling of the doses of hydrocortisone for the duration of illness and gradual tapering back to usual dose.

REFERRAL
All suspected cases, for full evaluation.

8.3 ANDROGEN DEFICIENCY
E29.1

DESCRIPTION
Reduced testosterone due to hypothalamic/pituitary hypofunction or primary testicular failure.

Investigations
» Morning (08h00–09h00) serum total testosterone.
» LH and FSH

	Serum testosterone	LH and FSH
Primary testicular failure	Below normal	Above normal
Secondary (hypothalamic/pituitary) hypogonadism	Below normal	Normal or below normal

Note: If the serum total testosterone concentration is borderline low repeat the test before replacement therapy is initiated. Don't test during serious illness.

» Measure serum prolactin
» Sperm count, if infertility is a consideration.
» Further investigations to determine cause to be undertaken after referral; consult a specialist.

MEDICINE TREATMENT

Screen hypogonadal men for prostate cancer before beginning testosterone replacement. Testosterone therapy can induce prostatic hypertrophy, polycythaemia, liver dysfunction, sleep apnoea and hyperlipidaemia. Baseline investigations for these are required prior to initiation of therapy and long-term surveillance is required.
Individualise dosage and review doses based on clinical response.

- Testosterone cypionate, deep IM, 200–300 mg every 2–4 weeks.
  - Monitor patients for prostate cancer during treatment.
  - Monitor haematocrit. If haematocrit ≥ 54%, stop testosterone therapy.

LoE:I[vii]

8.4 CUSHING SYNDROME

E24.0-4/E24.8-9

DESCRIPTION

Cushing syndrome is an illness resulting from excess cortisol secretion or exogenous glucocorticoid administration. Cushing disease is hypercortisolism secondary to an ACTH-secreting pituitary tumour.

Investigations

Low dose overnight dexamethasone suppression test (or when unavailable, betamethasone 1 mg equivalent to dexamethasone 1 mg).

- Dexamethasone, oral, 1 mg.
  - Administer at 23:00.
  - Measure plasma cortisol at 8:00, the next morning after breakfast.
  - In people with normal pituitary and adrenal function morning cortisol will be suppressed to <50 nmol/L.
  - Refer if cortisol levels >50 nmol/L.

LoE:III[viii]

GENERAL MEASURES

Check for hypertension and diabetes and treat accordingly.
Check potassium.

REFERRAL
All cases for investigation of aetiology and appropriate management.

8.5 DIABETES MELLITUS

DESCRIPTION
Types of diabetes:
» Type 1.
» Type 2.
» Other specific types, including pancreatic diabetes mellitus.
» Gestational diabetes mellitus: See Section 6.2: Diabetes mellitus in pregnancy.

GENERAL MEASURES
All patients require lifestyle modification.
Type 2 diabetes mellitus patients: weight loss if weight exceeds ideal weight.
Correct meal/energy distribution.
Moderate or no alcohol intake.
Encourage smoking cessation.
Increase physical activity, aim for 30 minutes per day 5 times a week.
Education about foot care is essential.
Manage comorbid depression. See Section 15.3.1: Depressive disorders.

Diagnosis
» In patients with symptoms of hyperglycaemia and any one of the following criteria:
  - Random plasma glucose ≥11.1 mmol/l; or
  - Fasting plasma glucose ≥7.0 mmol/l; or
  - 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥11.1 mmol/l.

» In asymptomatic patients any one of the following criteria, confirmed by a repeat test on a separate day within 2 weeks:
  - Fasting plasma glucose ≥7.0 mmol/l; or
  - 2-hour plasma glucose in a 75 g oral glucose tolerance test ≥11.1 mmol/l.

LoE:III[ix]

Classification:
After diabetes mellitus has been diagnosed, attempts must be made to classify the patient as type 1, type 2 or one of the other specific types (including pancreatic diabetes, genetic syndromes, infection and other causes). For management of gestational diabetes, see Section 6.2: Diabetes mellitus in pregnancy.

Monitoring

At every visit: *LoE:III[x]*

» Finger-prick blood glucose.
» Weight and calculation of body mass index.
» Waist circumference.
» Blood pressure.

Baseline:

» Serum creatinine concentration (and calculate estimated glomerular filtration rate (eGFR)).
» Serum potassium concentration, if on ACE-inhibitor or eGFR <30 mL/minute.
» Urine protein by dipstick.
  – If dipstick negative, request ACR, unless already on an ACE-inhibitor - microalbuminuria is defined as 2.5 to 25 mg/mmol in men, and 3.5 to 35 mg/mmol in women (see Section 8.7.2: Diabetic kidney disease).
  – If dipstick positive, see Section 8.7.2: Diabetic kidney disease.
» Blood lipids (fasting total cholesterol, triglycerides, HDL and LDL cholesterol).
» Foot examination.
» Eye examination to look for retinopathy.
» Waist circumference.

Measure HbA1c:

» 6-monthly in patients who meet treatment goals, and
» 3-monthly in patients whose control is sub-optimal or if therapy has changed, until stable.

Note: Monitoring of HbA1c implies that active clinical management will be implemented if the level is sub-optimal.

Annually:

» Serum creatinine concentration (and calculate eGFR).
» Serum potassium concentration (if on ACE-inhibitor/ eGFR <30 mL/minute).
» Urine protein by dipstick. *LoE:III[xi]*
  – If dipstick negative, request ACR, unless already on an ACE-inhibitor - microalbuminuria is defined as 2.5 to 25 mg/mmol in men, and 3.5 to 35 mg/mmol in women (see Section 8.7.2: Diabetic kidney disease).
  – If dipstick positive, see Section 8.7.2: Diabetic kidney disease.
» Eye examination to look for retinopathy.
» Foot examination.
» Assessment for peripheral neuropathy.
» Oral and dental examination.
» Assessment for macrovascular disease.
» Resting ECG.

TARGETS FOR CONTROL

Glycaemic targets for control:

Patient type	Target HbA1c	Target FPG*	Target PPG*
• Young, low risk • Newly diagnosed • No CVS disease	<6.5%	4.0–7.0 mmol/L	4.4–7.8 mmol/L
• Majority of patients	<7.0%	4.0–7.0 mmol/L	5.0–10.0 mmol/L
• Elderly • High risk • Hypoglycaemic unawareness • Poor short-term prognosis	<7.5%	4.0–7.0 mmol/L	<12.0 mmol/L

*FPG: fasting plasma glucose; PPG: post prandial plasma glucose.

Non-glycaemic targets:

» BMI ≤25 kg/m^2.
» BP ≤140/90 mmHg and ≥120/70 mmHg.

In the elderly, the increased risk of hypoglycaemia must be weighed against the potential benefit of reducing microvascular and macrovascular complications.

In patients with severe target organ damage, therapy should be tailored on an individual patient basis and should focus on avoiding hypoglycaemia.

REFERRAL

» Inability to achieve optimal metabolic control.
» Complications that cannot be managed on site, especially ophthalmic, e.g. cataracts and proliferative retinopathy.
» Recurrent severe hypoglycaemia.

8.5.1 TYPE 2 DIABETES MELLITUS

E11.0-9/E12.0-9/E13.0-9/E14.0-9

Management includes:

» Treatment of hyperglycaemia.
» Treatment of hypertension and dyslipidaemia after risk-assessment. See Section 3.6: Hypertension.
» Prevention and treatment of microvascular complications.
» Prevention and treatment of macrovascular complications.

MEDICINE TREATMENT

Oral blood glucose lowering drugs

Metformin is the preferred initial medicine and is added to the combination of dietary modifications and physical activity/exercise. If metformin, in maximal dose, with diet and exercise fails to lower HbA1c to target, a second agent should be added. This second agent may be either a sulphonylurea, or basal insulin. The specific indication is dependent on individual circumstances.

If a combination of two agents fails to lower HbA1c to target, a third agent is added. The preferential sequence of agents to use is metformin, followed by the addition of sulphonylurea, followed by the addition of basal insulin.

If the combination of two oral agents and basal insulin fails to lower HbA1c to target, or if other reasons to adjust therapy exist (such as nocturnal hypoglycaemia), then intensified insulin therapy in consultation with a specialist is required (either twice daily pre-mix, or basal-bolus therapy) and sulphonylureas are discontinued.

Note: Secondary failure of oral agents occurs in about 5–10% of patients annually.

Metformin

- Metformin, oral, 500 mg twice daily with meals.
  - Adjust dose based on fasting blood glucose levels and/or HbA1c to a maximum dose of 850 mg 8 hourly.
  - Monitor renal function. *LoE:I*[xii]
  - Dose-adjust in renal impairment as follows:

eGFR	Metformin dose
» eGFR >60 mL/min:	Normal daily dose (see above).
» eGFR 45–60 mL/min:	Standard dose, measure eGFR 3–6 monthly.
» eGFR 30–45 mL/min:	Maximum dose 1 g per day; measure eGFR 3–6 monthly.
» eGFR <30 mL/min:	Stop metformin.

  - Contra-indicated in:
    - renal impairment i.e. eGFR <30 mL/minute, *LoE:III*[xiii]
    - uncontrolled congestive cardiac failure,
    - severe liver disease,
    - patients with significant respiratory compromise, or
    - peri-operative cases.

Sulphonylurea derivatives: glimepiride or glibenclamide.

- Glimepiride, oral, 1 mg daily.
  - Titrate the dose by 1 mg at weekly intervals up to 6 mg daily (according to blood glucose levels). *LoE:III*[xiv]
  - Usual dose: 4 mg daily.
  - Maximum dose: 8 mg daily.

OR

- Glibenclamide, oral, 2.5 mg daily 30 minutes before breakfast.

- Titrate dose slowly depending on HbA1c and/or fasting blood glucose levels to 15 mg daily.
- When ≥7.5 mg per day is needed, divide the total daily dose into 2, with the larger dose in the morning.
- Avoid in the elderly and patients with renal impairment (i.e. eGFR <60 mL/minute).

LoE:III[xv]

Oral agents should not be used in type 1 diabetes and should be used with caution in liver and renal impairment.
Metformin should be dose adjusted in renal impairment.
Monitor patients on sulphonylurea derivatives and concomitant rifampicin and dose-adjust sulphonylurea as required. When rifampicin is discontinued, monitor for risk of hypoglycaemia and dose adjustment is required, particularly in the elderly.

Monitor serum creatinine and estimated eGFR three monthly in patients with kidney disease.

Insulin therapy in type 2 diabetes

Indications for insulin therapy:

» Inability to control blood glucose pharmacologically, i.e. combination/substitution insulin therapy.
» Temporary use for major stress, e.g. surgery, medical illness.
» Severe kidney or liver disease.
» Pregnancy.

Note:

» At initiation of insulin therapy, give appropriate advice on self-blood glucose monitoring (SBGM) and diet.
» It is advisable to maintain all patients on metformin once therapy with insulin has been initiated.

Insulin type	Starting dose	Increment	Max. daily dose
Add on therapy: • Intermediate to long-acting insulin	10 units, (or 0.3 units/kg/day), in the evening before bedtime, but not after 22h00.	If the starting dose is not effective increase by 2-4 units per dose every 3 to 7 days until fasting glucose is in the target range.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.
Substitution therapy: • Biphasic insulin (30/70 mix)	Total daily dose: 0.3 units/kg/day divided as follows: • 2/3 of total daily dose 30 minutes before breakfast. • 1/3 of total daily dose 30 minutes	4 units weekly. First increment is added to dose before breakfast.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.

Insulin type	Starting dose	Increment	Max. daily dose
	before supper. *LoE:III*[xvi]	Second increment is added to dose before supper.	
Basal bolus insulin therapy	Start with 0.4 to 0.6 units/kg and divide this total daily dose into 50% basal and 50% bolus, using equal pre-meal doses	Basal insulin is adjusted according to fasting glucose levels and bolus insulin is adjusted according to pre- and post-meal glucose, using the patient's home glucose record as a guide.	Refer if recurrent hypoglycaemia occurs and targets for control are not met.

Also see insulin protocols as in Section 8.5.2: Type 1 diabetes mellitus.

LoE:III[xvii]

Note: Insulin requirements decrease in patients with chronic renal impairment. In these situations, blood glucose monitoring must be done regularly (at least daily) in order to reduce the dose appropriately, reducing the risk of hypoglycaemia.

To reduce cardiovascular risk
See Section 8.8: Dyslipidaemia.

Renal impairment
If urine ACR >2.5 mg/mmoL (men) or >3.5 mg/mmoL (women):
Start treatment with a low dose of ACE-inhibitor and titrate up to the maximum tolerated dose.

ADD *LoE:I*[xviii]

- ACE-inhibitor, e.g.:
- Enalapril, oral.
  - Start with 5 mg 12 hourly and titrate to 20 mg 12 hourly, if tolerated (depending on BP and ACR). *LoE:III*[xix]

See Section 7.1.1: Chronic Kidney Disease.

If an ACE-inhibitor is not tolerated due to intractable cough, consider an angiotensin II receptor blocker. See Section 7.1.1: Chronic Kidney Disease.

8.5.2 TYPE 1 DIABETES MELLITUS

E10.0-9/ E12.0-9/E13.0-9/E14.0-9

Management includes:
» Maintenance of glycaemic control within acceptable limits.
» Prevention of chronic complications.
» Prevention of acute complications, e.g. hyperglycaemic and hypoglycaemic coma.

Insulin preparations

- Insulin, short acting SC, three times daily, 30 minutes before meals:
  Regular human insulin.
  Onset of action: 30 minutes.
  Peak action: 2–5 hours.
  Duration of action: 5–8 hours.
- Insulin, intermediate acting, SC, once or twice daily, usually at night, not later than 22h00.
  Onset of action: 1–3 hours.
  Peak action: 6–12 hours.
  Duration of action: 16–24 hours.
- Insulin, biphasic, SC, once or twice daily.
  Mixtures of regular human insulin and NPH insulin in different proportions, e.g. $^{30}/_{70}$.
  Onset of action: 30 minutes.
  Peak action: 2–12 hours.
  Duration of action: 16–24 hours.

Selection of insulin regimen

Basal bolus regimen

All type 1 diabetics should preferentially be managed with combined intermediate-acting (basal) and short-acting insulin (bolus), the so-called basal bolus regimen. This consists of pre-meal short-acting insulin and bedtime intermediate-acting insulin not later than 22h00.

Insulin doses

The initial total daily insulin dose:

- 0.6 units/kg body weight.

The total dose is divided into:

- 40–50% basal insulin
- The rest of the total daily dose (TDD) is given as bolus insulin split equally before each meal.

Adjust dose on an individual basis.

Alternative regimen where blood glucose cannot be measured frequently by the patient or caregiver: Twice daily insulin

Twice daily pre-mixed insulin, i.e. a mixture of intermediate- or short- acting insulin provides adequate control, when used with at least daily blood glucose monitoring.

Note: Optimal glycaemic control is seldom achieved with this regimen.

LoE:III

Insulin delivery devices

In visually impaired patients prefilled syringes should be used.

Home glucose monitoring

Patients on basal/bolus insulin should measure glucose 3-4 times daily. This may be individualised depending on the clinical need of the patient. *LoE:III*

All patients with type 2 diabetes, on insulin, should be given test strips for home glucose monitoring appropriate for their care plan.
It is important to maximise the value of home glucose monitoring by careful review of home glucose records at each visit and appropriate patient education in terms of self-dose adjustment.

LoE:I[xx]

Glucagon

Type 1 diabetics, who are found to be at high risk of hypoglycaemia because of recurrent episodes, should have a glucagon hypoglycaemia kit and both the patient and their family should be trained to use this emergency therapy.

Repeat prescriptions of glucagon hypoglycaemia kit should only be given if the kit has expired or been utilised.

LoE:III

8.6 DIABETIC EMERGENCIES

Diabetic emergencies includes hypyoglycaemia, diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar syndrome (HHS).

8.6.1 HYPOGLYCAEMIA

E10.0-1/E10.6/E11.0-1/E11.6/E12.0-1/E12.0-1/E12.6/E13.0-1/E13.6/E14.0-1/E14.6

Diagnosis: Clinical

Symptoms:

- » Anxiety
- » Palpitations
- » Headaches
- » Sweating
- » Hunger
- » Behavioural changes

Signs:

- » Sweating
- » Tachycardia
- » Bizarre neurological signs
- » Coma
- » Tremor
- » Confusion
- » Seizures

Biochemical

Act on finger prick blood glucose. Confirm with laboratory measurements if uncertain.

TREATMENT

Start immediately.

- Dextrose 50%, rapid IV injection, 50 mL.

Assess clinical status and finger prick glucose level over the next 5–10 minutes.

LoE:III[xxi]

Establish a large bore intravenous line and keep open with:

- Dextrose 10%, IV.

If no clinical response, give a second injection of:

- Dextrose 50%, IV, 50 mL.

To prevent recurrent hypoglycaemia, continue infusion with:

- Dextrose 10%, IV infusion, at a rate of ± 1 L 6 hourly.

Once blood glucose is normal or elevated, and the patient is awake, check blood glucose hourly for several hours, and check serum potassium for hypokalaemia.

If the patient has not regained consciousness after 30 minutes with normal or elevated blood glucose, look for other causes of coma.

Once the patient is awake, give a snack if possible, and **admit** for observation and education etc., to prevent further hypoglycaemic episodes.

> If hypoglycaemia was caused by a sulphonylurea, the patient will require hospitalisation and a prolonged intravenous glucose infusion.
>
> Observe patient for at least 12 hours after glucose infusion has stopped.

Recurrent hypoglycaemia

In cases of recurrent hypoglycaemia consider:

» inappropriate management, e.g. too much insulin or too high dose of sulphonylurea,
» poor meal adherence,
» poor adherence,
» alcohol abuse,
» physical exercise,
» factitious administration of insulin,
» the “honeymoon” period of type 1 diabetes,
» the advent of renal failure,
» hypoglycaemic unawareness, or
» pancreatic diabetes/malabsorption.

Other causes of hypoglycaemia should also be considered e.g. associated Addison’s disease or hypopituitarism.

Recurrent hypoglycaemia may be the cause of hypoglycaemic unawareness, which may occur in patients with type 1 diabetes. The loss of warning symptoms can lead to severe hypoglycaemia. In some cases, this situation can be restored to normal with avoidance of any hypoglycaemia for at least 2–4 weeks.

8.6.2 DIABETIC KETOACIDOSIS (DKA) AND HYPEROSMOLAR HYPERGLYCAEMIC STATE (HHS)

E10.0-1/E11.0-1/E12.0-1/E13.0-1/E14.0-1

Diabetic comas – recognition and clinical profiles

DKA often occurs in younger patients and develops over hours to days. There may be vomiting, abdominal pain and acidotic breathing.

» blood glucose usually <40 mmol/L
» blood ketones are positive
» serum osmolality <350 mOsm/L

Hyperosmolar hyperglycaemic state (HHS) is a syndrome characterised by impaired consciousness, sometimes accompanied by seizures, extreme dehydration and severe hyperglycaemia, that is not accompanied by severe ketoacidosis (pH usually >7.2). It usually occurs in elderly type 2 diabetic patients and develops over days to weeks.

» Blood glucose usually >40 mmol/L.
» Blood ketones usually negative to moderately elevated.
» Urine ketones may be positive.
» Serum osmolality is >320 mOsm/L.

Anion gap = Na – (Cl + HCO_3) (Normal = ± 12: DKA >20).
Calculated serum osmolarity = 2 (Na + K) + glucose + urea.

GENERAL MEASURES

All patients:

» Set up an intravenous line.
» Protect airway and insert a nasogastric tube, if unconscious.
» Monitor urine output.
» Monitor plasma glucose, ketones, urine, electrolytes and venous blood gas.
» Look for precipitating causes, e.g. infection or MI.

MEDICINE TREATMENT

Fluids

Average deficit 6 L, may be as much as 12 L.
If renal or cardiac disease is present, monitor with central venous pressure.
In the absence of renal or cardiac compromise:

- Sodium chloride 0.9%, IV, 15–20 mL/kg in the first hour.
  - Patients <20 years of age: initial volume of 10–20 mL/kg in the 1st hour.
  - Subsequent infusion rate varies from 5–15 mL/kg/hour depending on the clinical condition.
  - Correction of estimated deficits should take place over 24 hours.
  - The volume infused in the first 4 hours should not exceed 50 mL/kg.
  - Fluid therapy thereafter is calculated to replace the estimated deficit in 48 hours, ± 5 mL/kg/hour.
  - Reduction in serum osmolality should not exceed 3 mOsm/kg/hour.

Correct plasma sodium value for blood glucose.
[Rough guide: divide glucose by 3 and add to sodium value.]

If plasma Na^+ >140 mmol/L:
- Sodium chloride 0.45%, IV.

If plasma Na^+ ≤140 mmol/L:
- Sodium chloride 0.9%, IV.

If plasma glucose <15 mmol/L, but ketones still present:
- Dextrose 5% **or** dextrose 10% in sodium chloride 0.9%, IV.

LoE:III[xxii]

Note:
» Adjust fluid volumes according to clinical criteria.
» Cerebral oedema may occur with over-aggressive fluid replacement or rapid sodium change.

Potassium

Potassium will fall on insulin treatment and patients with DKA have potassium depletion even if initial potassium is normal or high.
It is therefore essential to monitor and replace potassium.

Total body deficit 300–1 000 mmol.
(1 ampoule = 20 mmol = 10 mL)

- Potassium chloride, IV, added to 1 L of fluid.
  - potassium <3.5 mmol/L: add 40 mmol (2 ampoules).
  - potassium 3.5–5.5 mmol/L: add 20 mmol (1 ampoule).
  - potassium >5.5 mmol/L: do not add any potassium.

  Maximum potassium dose: 40 mmol/hour.
  Monitor potassium hourly initially, then 2 hourly when stabilised.

LoE:III

If serum potassium results are not readily available:
- Potassium chloride, IV, 20 mmol (1 ampoule) added to 1 L of fluid as soon as **the patient has established adequate urinary output.**

Bicarbonate
There is no proven role for the use of intravenous sodium bicarbonate and it could potentially cause harm.

Insulin therapy
Patients should be preferentially managed with continuous intravenous infusions or hourly intramuscular injections (see below) in a high care ward, with appropriate monitoring.

Note:
» Ketonaemia takes longer to clear than hyperglycaemia and combined insulin and glucose (and K+) are needed to ensure clearance of ketonaemia.
» Avoid focusing on glucose control alone!
» Continue insulin until acidosis and ketosis have resolved.

Continuous intravenous infusion:
- Insulin, **short-acting,** IV infusion, 50 units in 200 mL sodium chloride 0.9%.
  - 4 mL solution = 1 unit insulin.
  - Initial infusion: 0.1 unit/kg/hour.
  - Usually 5–7 units/hour: 20–28 mL/hour.
  - If plasma glucose does not fall by 3 mmol/L in the 1st hour, double the insulin infusion (hourly) until a steady reduction of plasma glucose is achieved, i.e. at least 3–4 mmol/L per hour.
  - If plasma glucose <14 mmol/L, reduce insulin infusion rate to 1–2 units/hour and adjust subsequently according to hourly bedside capillary glucose level measured with glucose test strips.

Hourly intramuscular bolus injections:
Where intravenous infusion cannot be safely administered:
- Insulin, **short-acting**
  - Dilute 100 units with sodium chloride 0.9% to 10 mL i.e. 10 units/mL.
  - Loading dose: 0.5 units/kg body weight.
  - Administer half the dose as an intravenous bolus injection and the other half IM. Do not administer with an insulin syringe and needle.
  - Subsequent hourly doses: ± 5–10 units IM every hour (i.e. 0.1 units/kg/hour) and titrated against the bedside capillary glucose level.

Progress management
Continue insulin therapy until the acidosis has resolved and:
- the patient is able to eat, and
- subcutaneous insulin therapy is instituted either at previous doses or, for newly diagnosed diabetes at 0.5–1 unit/kg total daily dose divided into at least 2 doses with mixed short- and long-acting insulin (biphasic insulin $^2/_3$ in the morning and $^1/_3$ at night).

Infusion must overlap with subcutaneous regimen for 1–2 hour to avoid reversion to keto-acidosis.

Heparin.
For all patients**:**
- Low molecular weight heparin, e.g.:
- Enoxaparin, SC, 40 mg daily.

LoE:I[xxiii]

OR

- Unfractionated heparin, SC, 5 000 units 12 hourly.

8.7 COMPLICATIONS OF DIABETES

Macrovascular complications
Diabetic patients with a history of myocardial infarction, vascular bypass, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina need secondary prevention with aspirin and a statin – see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

Hypertension
See Section 3.6: Hypertension.

Dyslipidaemia
See Section 8.8: Dyslipidaemia.

8.7.1 DIABETIC NEUROPATHIES

E10.4† / E11.4† + (G63.2*/G99.0*/G59.0*)

DESCRIPTION

Neuropathies are a common complication of diabetes. They play an important role in the morbidity and mortality suffered by people with diabetes.

There are three major categories:
» peripheral neuropathy,
» autonomic neuropathy, and
» acute onset neuropathies.

MEDICINE TREATMENT

Ensure appropriate glycaemic control.
Exclude or treat other contributory factors e.g.:
» alcohol excess,
» vitamin B_{12} deficiency, if suspected,
» uraemia, and
» HIV infection.

Pain
See Section 26.1.4: Management of neuropathic pain.

Gastroparesis

- Metoclopramide, oral, 10 mg 8 hourly, 30 minutes before meals.

If ineffective, consult a specialist.

8.7.2 DIABETIC KIDNEY DISEASE

E10.0/E11.2/E12.2/E13.2/E14.2 + (N18.1-5/N18.9)

See Section 7.1.1: Chronic Kidney Disease.

8.7.3 DIABETIC FOOT ULCERS

L97/L08.8 + (E10.5/E11.5/E12.5/E13.5/E14.5)

GENERAL MEASURES

Metabolic control.
Treat underlying comorbidity (e.g.: corns, alcohol misuse, ingrown toenails).
Relieve pressure: non-weight bearing is essential.
Smoking cessation is essential.

Deep (limb-threatening) infection
X-ray of affected limb.
Surgical drainage as soon as possible with removal of necrotic or poorly vascularised tissue, including infected bone – **refer urgently.**
Revascularisation, if necessary.

Local wound care
Frequent wound debridement with scalpel, e.g. once a week.
Frequent wound inspection.
Absorbent, non-adhesive, non-occlusive dressings.

Superficial ulcer with extensive infection
Debridement with removal of all necrotic tissue.

MEDICINE TREATMENT

Superficial ulcer with extensive infection

Antibiotic therapy
For polymicrobial infection:
Topical antibiotics are not indicated.

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 10 days.
  - Longer course of therapy may be necessary.

Severe infection
- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly.

Severe penicillin allergy (Z88.0)
- Clindamycin, oral, 150–450 mg 8 hourly.

AND
- Gentamicin, IV, 6 mg/kg daily (see Appendix II for guidance on prescribing).

REFERRAL
Arterial revascularisation procedures.

8.8 DYSLIPIDAEMIA
E78.0-9/E78.8-9

DESCRIPTION
Non-pharmacological therapy plays a vital role in the management of dyslipidaemia. Many patients with mild or moderate dyslipidaemia will be able to achieve optimum lipid levels with lifestyle modification alone and may not require lifelong lipid modifying therapy.

Accompanying modifiable risk factors for coronary artery disease (CAD) e.g. hypertension, smoking, diabetes, must be sought and treated.

Underlying causes of secondary dyslipidaemia, e.g. excess alcohol intake, hypothyroidism, should be identified and corrected.

The goal of treatment should be explained clearly to the patient and the risks of untreated dyslipidaemia should be emphasised.

GENERAL MEASURES
Lifestyle modification
Dietary strategies are effective.
» Replace saturated fats with unsaturated fats (mono-and polyunsaturated fats) without increasing calories from fats.
» Consume a diet high in fruits, vegetables, nuts and whole unrefined grains.
Smoking cessation.
Increase physical activity.
Maintain ideal body weight.

MEDICINE TREATMENT
Indication for medicine therapy
Cardiovascular
The main indication for lipid-modifying medication is to reduce the risk of a cardiovascular event. Medicine therapy should be considered when non-pharmacological means have failed to reduce the lipid levels to within the target range. When lipid-lowering medicines are used, this is **always** in conjunction with ongoing lifestyle modification.

Patients with any of the following factors are at a relatively high risk for a cardiovascular event and would benefit from lipid lowering therapy:
» established atherosclerotic disease
  - confirmed ischaemic heart disease
  - peripheral vascular disease
  - atherothrombotic stroke
» type 2 diabetics with age >40 years of age

» type 1 diabetes with microalbuminuria
» diabetes with chronic kidney disease (eGFR <60 mL/minute). LoE:I[xxiv]

Patients without established vascular disease, with a risk of MI ≥20% in 10 years: lifestyle modification and start statin treatment - see Section 3.1: Ischaemic heart disease and atherosclerosis, prevention.

Non-cardiovascular

The most serious non-cardiovascular complication of dyslipidaemia is the development of acute pancreatitis. This is seen in patients with severe hypertriglyceridaemia (fasting triglycerides >10 mmol/L). Ideally such patients should be discussed with a lipid specialist.

Fibrates are the medicines of choice for severe hypertriglyceridaemia not due to secondary causes.

Choice of medication

Depends on the type of lipid disturbance:

» predominant hypercholesterolaemia: statin
» mixed hyperlipidaemia: statin or fibrate
» predominant hypertriglyceridaemia: fibrate

- HMGCoA reductase inhibitors (statins), according to table below:

INDICATION	HMGCOA REDUCTASE INHIBITOR (STATIN) DOSE
A: Primary prevention - no existing CVD	
» Type 2 diabetes with age >40 years. » Diabetes for >10 years. » Diabetes with chronic kidney disease. » ≥20% 10-year risk of cardiovascular event.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night.
» Patients on protease inhibitors. (Risks as above, after switching to atazanavir – see Section below).	• Atorvastatin, oral, 10 mg at night.
B: Secondary prevention – existing CVD	
» Ischaemic heart disease. » Atherothrombotic stroke. » Peripheral vascular disease.	▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 40 mg at night LoE:I[xxv]
» Patients on protease inhibitors.	• Atorvastatin, oral, 10 mg at night. LoE:I[xxvi]
» Patients on amlodipine (and not on protease inhibitor).	• Simvastatin, oral, 10–20 mg at night. LoE:III[xxvii]

» If patient complains of muscle pain.	Reduce dose: ▪ HMGCoA reductase inhibitors (statins), e.g.: • Simvastatin, oral, 10 mg at night. **OR** Consult specialist for further management. *LoE:III*[xxviii]

Note: Lipid-lowering medicines must always be used in conjunction with ongoing lifestyle modification.

For patients with moderate to severe fasting hypertriglyceridaemia and for patients on antiretroviral therapy i.e. triglycerides >10 mmol/L:

- ▪ Fibrates, e.g.:
- • Bezafibrate, slow release, oral, 400 mg daily.

Aspirin therapy:

Use in adult patients with diabetes who have a history of cardiovascular disease i.e.

- ischaemic heart disease
- peripheral vascular disease
- previous thrombotic stroke

- • Aspirin, oral, 150 mg daily. *LoE:I*[xxix]

Dyslipidaemia in HIV-infected patients: See Section 10.1.2: Management of selected antiretroviral adverse drug reactions.

REFERRAL

» Patients with possible familial hypercholesterolaemia (FH) i.e. random cholesterol >7.5 mmol/L or with tendon xanthomata (See Section 3.1: Ischaemic heart disease and atherosclerosis).
» Suspected severe familial dyslipidaemias.

8.9 HYPERCALCAEMIA, INCLUDING PRIMARY HYPERPARATHYROIDISM

E83.5 + (E21.0/D71)

DESCRIPTION

When serum calcium (corrected for albumin) concentrations exceed the upper limit of normal.

Aetiology

» Ambulatory patients: most common cause is hyperparathyroidism (>90% of cases).
» Hospitalised patients: malignancies are the most common cause (65% of cases). Hyperparathyroidism accounts for another 25%.
» Granulomatous disease (e.g. sarcoid).

» Immobilisation in those with high bone turnover.

Investigations
Draw blood for parathyroid hormone (PTH) and simultaneous calcium, phosphate, magnesium, albumin, creatinine and sodium and potassium, and 25 hydroxy-vitamin D concentrations.
A detectable PTH in the presence of hypercalcaemia indicates PTH-dependent hyperparathyroidism.

MEDICINE TREATMENT
Hypercalcaemia
Patients with moderate/severe hypercalcaemia should be kept well hydrated and may need several litres of fluid.

Avoid thiazide diuretics in the acute setting as they increase serum calcium concentration.

The addition of furosemide has not been shown to be of benefit.

For symptomatic hypercalcaemia:
- Sodium chloride solution 0.9%, IV infusion, 4–6 L in 24 hours.
  - Monitor urine output.

If still symptomatic after 24 hours and adequate hydration, **or** if initial serum calcium is >3 mmol/L:
ADD
- Bisphosphonates, e.g.:
- Zoledronic acid, IV infusion, 4 mg over 15 minutes (specialist initiated).
  - eGFR 35 to 60 mL/minute, adjust dose in consultation with specialist.
  - **Note**: Do not use if eGFR <35 mL/minute. *LoE:I*[xxx]

In patients with granulomatous disease and haematological malignancies:
- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg depending on response, daily.

LoE:III[xxxi]

REFERRAL
When a diagnosis of hyperparathyroidism is confirmed or other cause is not obvious.

8.10 HYPOCALCAEMIA
E83.5 + (E20.0-1/E20.8-9)

DESCRIPTION
Serum calcium (corrected for albumin) below the lower limit of normal.
Causes
» Renal failure.
» Hypoparathyroidism:

  - post neck surgery,
  - radiotherapy, or
  - idiopathic.
» Vitamin D-related, (deficient intake, activation or action).
» Hypomagnesaemia.
» Malabsorption syndrome.

MEDICINE TREATMENT
Therapy is aimed at treating the underlying cause.

For acute hypocalcaemia with neurological problems and prolonged QT time on ECG:

- Calcium gluconate 10%, infusion, 20 mL in 100 mL dextrose 5% given over 20 minutes, with ECG monitoring.

AND

- Calcium gluconate 10%, infusion, 15 mg/kg (= wt [kg] x 1.7 mL) in 1000 mL sodium chloride 0.9% over 4 hours.

LoE:III[xxxii]

For hypoparathyroidism:

- Alfacalcidol, oral, 1–3 mcg daily.

AND

- Calcium, elemental, oral, 500–1 500 mg daily in divided doses.

Correct magnesium deficiency if present.

Renal failure:
See Section: 7.1.1 Chronic Kidney Disease (CKD).

REFERRAL
» If cause is uncertain.
» If hypoparathyroidism suspected and PTH analysis required as above.

8.11 HYPOTHYROIDISM
E03.0-5/E03.8-9

DESCRIPTION
Causes
Common causes of primary hypothyroidism are:
» chronic autoimmune thyroiditis,
» post-surgery, and
» post radio-active iodine.
Secondary hypothyroidism (less than 1% of cases) may be due to any cause of anterior hypopituitarism.

Investigations
Thyroid stimulating hormone (TSH) and thyroxine (T_4) initially. In primary hypothyroidism TSH is elevated and T_4 is low. If TSH is normal or slightly elevated and T_4 is low this suggests hypopituitarism: take blood for cortisol and ACTH, give hydrocortisone replacement before starting levothyroxine and investigate for causes of hypopituitarism.

MEDICINE TREATMENT

- Levothyroxine, oral, 100 mcg daily.
  - If there is a risk of ischaemic heart disease, start at 25 mcg daily and increase by 25 mcg every 4 weeks.

Check TSH and T_4 after 2–3 months and adjust dose if required.
TSH levels will take several weeks to stabilise. Once stable check T_4 and TSH annually.

Hypothyroidism in pregnancy
About 60% of hypothyroid pregnant women need an increase in levothyroxine therapy in the second and third trimesters. Because T_4 takes a long time to reach steady state and 1st trimester hypothyroidism is undesirable for the fetus, for patients with borderline control (TSH>1.2mU/L) it is advisable to increase the pre-pregnancy dose by 30%. Check TSH monthly and increase levothyroxine doses to keep serum TSH levels low normal and free T_4 levels in the high-normal range. After delivery, revert to pre-conception doses.
Note: TSH and T_4 reference range is trimester-specific.

LoE:II[xxxiii]

8.12 OSTEOPOROSIS

M80.00-59/M80.80-99/M81.00-69/M81.80-99/M82.00-19/M82.80-89

DESCRIPTION

A disease characterised by low bone mass and micro-architectural bone deterioration leading to bone fragility and increase in fracture risk.

GENERAL MEASURES

Prevention
Adequate energy and protein intake.
Adequate dietary calcium intake (>1 g/day) particularly in the young, in breastfeeding mothers and in the elderly. This is preferably obtained from a dietary source.
Weight bearing exercises, e.g. brisk 30-minute walk 3 times a week.
Smoking cessation.
Avoid excessive alcohol intake - >2 units daily has a 40% increased risk of sustaining any osteoporotic fracture, compared to people with moderate or no alcohol intake.
Avoid falls.

LoE:III[xxxiv]

MEDICINE TREATMENT

Primary prevention

In institutionalised frail elderly patients, supplementation with calcium and vitamin D may reduce the incidence of hip fractures:

- Calcium, elemental, oral, 1 000 mg daily.

AND

- Vitamin D (Calciferol), oral, 800 units daily **or** 50 000 of Calciferol every 4 weeks. *LoE:III*[xxxv]

Note: Routine supplementation with calcium and vitamin D marginally increases the risk of myocardial infarction and stroke and is of unclear benefit in other populations. *LoE:I*[xxxvi]

Secondary prevention

Secondary prevention of osteoporotic fracture, including patients on long-term corticosteroids:

In severe osteoporosis, i.e. patients who have a T-score of –2.5 (severe osteoporosis) plus an osteoporotic fracture:

- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

LoE:I[xxxvii]

Supplement with:

- Calcium, elemental, oral, 1 000mg daily.

AND

- Vitamin D (Calciferol), oral, 800 units daily.

Hormone replacement therapy

See Section 5.12: Menopause and Perimenopausal Syndrome.
Only indicated early in menopause, if vasomotor symptoms are significant.
Review contra-indications before initiating therapy.

REFERRAL

» To establish diagnosis (bone densitometry).
» For initial assessment.
» Initiation of, and monitoring response to, therapy, and 18–24 monthly bone mineral density (BMD).
» Fractures suspected to be due to osteoporosis for consideration for alendronate.
» Patients not tolerating oral bisphosphonate.
» Patients with e-GFR < 30 mL/minute.

8.13 OSTEOMALACIA/RICKETS

M83.00-59/M83.80-99/E55.0

DESCRIPTION

A disorder of mineralisation of newly synthesised bone matrix.

REFERRAL

All patients.

8.14 PAGET'S DISEASE

M88.08/M88.80-99

DESCRIPTION

Bone disease characterised by localised uncontrolled formation of highly active osteoclasts leading to an increase in bone resorption followed by chaotic increase in bone formation.

GENERAL MEASURES

Most cases are mild and asymptomatic and no treatment is required. The diagnosis is supported by isolated high alkaline phosphatase and typical CXR radiological changes.

Avoid high calcium diet when immobile as hypercalcaemia may occur with immobilisation.

Differentiate bone pain of Paget's, especially at night, from arthritic pain in joints near deformed bone, e.g. hip and knee joints, as well as pain resulting from fracture or complicating osteosarcoma.

MEDICINE TREATMENT

For arthritic pain:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

REFERRAL

All patients.

8.15 PITUITARY DISORDERS

Includes prolactinoma, anterior hypothyroid hypopituitarism and diabetes insipidus.

8.15.1 PROLACTINOMA

D35.2 + (M8271/0)

DESCRIPTION

Prolactinoma is the most common functioning pituitary tumour.

Investigations
Serum prolactin, β-hCG.

Note:
» There are numerous causes of hyperprolactinaemia other than a prolactinoma, so secondary causes must be excluded e.g. pregnancy, medicines, physiological, hypothyroidism, chronic renal failure and tumours.
» In patients with prolactinoma, serum prolactin levels are usually elevated ≥4 times the upper limit of the normal reference range for the laboratory method used. Lesser degree of elevation of serum prolactin may also be found in patients with other pituitary tumours associated with pituitary stalk compression.

MEDICINE TREATMENT
Dopamine agonist therapy is the treatment of choice.
- Bromocriptine, oral, 1.25 mg at bedtime with a snack.
  - Initial maintenance dose: increase dose to 2.5 mg 12 hourly with food and check prolactin 4 weeks later.
  - Higher doses may be needed.
  - GIT side effects are minimised by giving doses with food.
  - If total dose of 10 mg does not normalise prolactin, refer.

REFERRAL
» All tumours, once causes of secondary hyperprolactinaemia have been sought and excluded.
» Intolerance to bromocriptine.
» Unexplained hyperprolactinemia.

Urgent
» Any visual disturbances, **especially those** suggesting compression of optic chiasm.
» Pituitary apoplexy.

8.15.2 ANTERIOR HYPOPITUITARISM
E23.0-3/E28.3/E29.1

DESCRIPTION
Absent or diminished secretion of one or more anterior pituitary hormones due to primary damage of the anterior pituitary gland, or secondary to hypothalamic dysfunction, which may result in hypothyroidism and/or hypoadrenalism and/or hypogonadism or growth retardation in children.

GENERAL MEASURES
Surgery is required for large tumours, pituitary apoplexy, and hormone secreting tumours (except for most patients with prolactinomas, who generally

respond well to medical therapy).
Radiotherapy may be required in selected patients.
A notification bracelet is needed.

MEDICINE TREATMENT

Acute crisis
Treat as for acute crisis in Section 8.2: Adrenal Insufficiency (Addison's Disease).

Chronic
See Section 8.2: Adrenal Insufficiency (Addison's Disease).

Hypoadrenalism
See Section 8.2: Adrenal Insufficiency (Addison's disease) and 8.11: Hypothyroidism.

Hypothyroidism
See Section 8.11: Hypothyroidism.

Hypogonadism
Individualise dosage and need for replacement according to age, symptoms, etc.

Women:
As for postmenopausal HT, see Section 5.12: Menopause and perimenopausal syndrome.

Men:
- Testosterone cypionate, IM, 200–300 mg every 3–4 weeks.

See Section 8.3: Androgen deficiency.

REFERRAL

All diagnosed patients for initial assessment.

8.15.3 DIABETES INSIPIDUS (POSTERIOR HYPOPITUITARISM)

E23.2

DESCRIPTION

Damage to the posterior pituitary leading to deficient production of antidiuretic hormone. Characterised by the passage of large amounts of dilute urine, usually >2.5 litres daily.
Causes include head trauma and neurosurgery but most cases are idiopathic.
Consultation with a specialist is recommended.

GENERAL MEASURES

Rehydration with water or hypotonic fluids.

MEDICINE TREATMENT

Postoperative or acutely ill patients:

- Desmopressin, IV/SC, 2–4 mcg daily, either as a single dose or in 2 divided doses.

OR

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.

OR

- Desmopressin, oral, 0.05 mg, 8–12 hourly.
  - Optimal dose: 0.1–0.8 mg daily.
  - Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

If patient has a normal thirst mechanism, and does not receive IV fluids for other purposes:

» oral, intranasal, or IV/SC dosing can be used; and
» keep urine osmolality at 450–600 mOsm/kg.

If patient requires IV fluids and/or is unable to regulate total fluid intake by thirst mechanism:

» IV dosing is preferred; and
» continually adjust the level of antidiuresis to maintain hydration and plasma sodium within the normal.

Replacement therapy:

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.
  - Adjust morning and evening doses separately for appropriate diurnal rhythm of water turnover.

OR

- Desmopressin, oral, 0.05 mg, either as a single dose or in 2–3 divided doses.
  - Optimal dose: 0.1–0.8 mg daily.
  - Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

LoE:III[xxxviii]

REFERRAL

All patients diagnosed or suspected.

Water deprivation may be necessary to confirm the diagnosis. Careful monitoring of electrolytes and exclusion of fluid overload while on therapy is essential to determine the appropriate dose.

8.16 PHAEOCHROMOCYTOMA

C74.0-1/C74.9/C79.7/D09.3/D35.0/D44.1 + (M8700/0/3/6)

Description

Catecholamine-secreting tumour of the adrenal medulla.

Clinical presentation

Always consider in hypertensive patients who have paroxysmal symptoms:

- » headaches,
- » GIT symptoms,
- » palpitations,
- » anxiety.
- » tremor,
- » recurrent chest discomfort,
- » sweating, and

There is marked inter-individual variation in symptoms.
Patients may also have orthostatic changes in BP.

Diagnosis

24-hour urine acidified with HCl: normetanephrine (NMA), vanillylmandelic acid (VMA), should be ≥ twice normal for a definite diagnosis. Test is best done during a paroxysm, if possible, using at least 2 samples.
There are many drugs, foods and diseases that can falsely elevate or lower NMA/VMA levels; therefore, the clinician must interpret the results in the light of the clinical context and after having taken an accurate history.

Screen:

- » young hypertensive patients;
- » hypertensive patients with paroxysmal symptoms; and
- » patients with:
  - — The classic triad of headache, sweating, and tachycardia, whether or not they have hypertension
  - — a family history of a phaeochromocytoma,
  - — A familial syndrome that predisposes to catecholamine-secreting tumours (e.g., multiple endocrine neoplasia type 2 [MEN2], neurofibromatosis type 1 [NF1], or von Hippel-Lindau [VHL]). or
  - — radiologic evidence of an adrenal mass (adrenal incidentaloma) with or without hypertension.

GENERAL MEASURES

Surgical removal of the tumour.

MEDICINE TREATMENT

Once diagnosis is confirmed, initiate medication with immediate referral.

- Alpha blockers, e.g.:
- Doxazosin, oral, 4 mg daily.
  - Dose increase above 8 mg daily to control blood pressure may be required.

LoE:III[xxxix]

- Calcium channel blockers may be added, e.g.:

- Amlodipine, oral, 5–10 mg daily.

Note:
» Do not give patients diuretic therapy unless pulmonary oedema is present.
» β-blockers must be used with extreme caution in the management of phaeochromocytoma, and only after adequate alpha blockade.

LoE:III[xi]

REFERRAL
All patients.

8.17 PRIMARY ALDOSTERONISM
E26.0

DESCRIPTION
Increased aldosterone production usually due to an adrenal adenoma (Conn's syndrome) or idiopathic bilateral adrenal hyperplasia (the majority of cases).

Clinical
Suspect in a patient with resistant hypertension or hypertension with hypokalaemia.

Diagnosis
Elevated serum aldosterone with a suppressed renin level **and** elevated aldosterone/renin ratio.
ACE-inhibitors, angiotensin receptor blockers (ARBs), and diuretics can give falsely elevated or lowered results. Stop all these drugs for a minimum of 2 weeks before testing. Stop spironolactone for 6 weeks before testing.

Because of limited specificity, a positive screening test result should be followed by a confirmatory test. A negative random ratio test does not necessarily exclude the diagnosis.

MEDICINE TREATMENT
Adrenal adenoma
A surgical reSection/removal of adenoma.

Bilateral hyperplasia
Standard anti-hypertensive therapy, including spironolactone.
- Spironolactone, oral, 100–200 mg daily.

REFERRAL
All patients to an endocrinologist or a hypertension centre for confirmation of the diagnosis and further treatment.

8.18 HYPERTHYROIDISM

E05.0-5/E05.8-9

DESCRIPTION

Most common cause of hyperthyroidism is Graves' disease, which is an autoimmune condition resulting from the presence of thyroid stimulating autoantibodies. Other common causes are toxic single or multinodular goitre and sub-acute thyroiditis. Thyrotoxicosis in the setting of any other acute life-threatening condition such as cardiac failure etc. should be managed as thyroid crisis – see Section 8.18.5: Thyroid crisis.

Investigation

TSH and free T_4.
If TSH suppressed and free T_4 normal, request free T_3.
The usual biochemical abnormalities are: low TSH, elevated free $T_{4/3}$.
TSH receptor antibodies should be measured in all patients.

Once thyrotoxicosis is confirmed, if cause is uncertain request thyroid uptake scan. If uptake is:

» Elevated or diffuse: Grave's disease.
» Markedly decreased: Thyroiditis.
» Patchy uptake with areas of increased uptake: Toxic multinodular goitre.

REFERRAL

» Consultation with a specialist is recommended in all cases.
» For thyroid scan if necessary.
» Thyroid-associated ophthalmopathy.
» When radioactive iodine or surgery is contemplated.
» If patient is pregnant.

8.18.1 GRAVES' HYPERTHYROIDISM

E05.0

MEDICINE TREATMENT

- Carbimazole, oral, 20–40 mg daily.
  - Titrate dose according to thyroid hormone levels (T_4).
  - Duration of therapy: 12–18 months.
  - Durations of therapy longer than 12 months must be in consultation with a specialist.

ß–blockers

» Used to counteract excessive sympathetic symptoms, e.g. palpitations.
» Dose is titrated according to the heart rate.
» Give for 2–6 weeks, together with carbimazole until T4 levels normalise.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily.

- Titrate according to symptom control up to 100 mg daily. LoE:III[xli]

Radioactive iodine
In the setting of Graves' disease radioactive iodine may be administered for failed medical therapy and may be indicated for patients with coexistent heart disease. Refer patient if radioactive treatment is contemplated.

Surgery
Seldom indicated, but to consider in the following situations: large thyroid causing obstructive symptoms, failure of anti-thyroid medicine therapy, allergy to anti-thyroid therapy, 2nd trimester of pregnancy, and not responding to or allergic to anti-thyroid medication.

Monitoring
Patients with Graves' disease who are treated with anti-thyroid drugs should be monitored every 6–8 weeks using a serum T_4. TSH may remain suppressed for months. Once in remission, patients may be monitored less frequently to determine signs and symptoms of recrudescence of thyrotoxicosis.

Because there is a risk of neutropenia or agranulocytosis with carbimazole, therapy should be temporarily stopped and a white cell count (with differential) must be done in patients presenting with an infection or sore throat.

Post-radio-active iodine TSH and free T_4 should be checked at 6 weeks, 3, 6, 9 and 12 months and annually thereafter until either hypothyroidism occurs or patient remains euthyroid for ± 3–4 years. Although uncommon, new onset hypothyroidism can occur years later.

8.18.2 TOXIC MULTINODULAR GOITER
E05.2

MEDICINE TREATMENT
Radio-active iodine
Radioactive iodine is the treatment of choice. Medical therapy is indicated initially for patients with underlying heart disease to achieve euthyroidism before radio-active iodine. Surgery is restricted to patients with obstructive symptoms.

8.18.3 SINGLE TOXIC NODULES
E05.1

MEDICINE TREATMENT
Radioactive iodine
Smaller nodules are best managed with radio-active iodine while larger nodules may require surgery.

ß–blockers
» Used to counteract excessive sympathetic symptoms, e.g. palpitations.
» Dose is titrated according to the heart rate.
» Give for 2–4 weeks.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily.
  - Titrate according to symptom control up to 100 mg daily.

8.18.4 THYROIDITIS

E06.0-5/E06.9

Toxic phase lasts up to 3 months.

MEDICINE TREATMENT

ß–blockers

Used to counteract excessive sympathetic symptoms, e.g. palpitations.
Dose is titrated according to the heart rate.
Give for 2–4 weeks.

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily
  - Titrate according to symptom control up to 100 mg daily.

For painful subacute thyroiditis (De Quervain's): E06.1

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily (Specialist consultation). *LoE:III*[xlii]

8.18.5 THYROID CRISIS

E05.5

MEDICINE TREATMENT

IV fluids as indicated.

- Carbimazole, oral, 40–60 mg 6 hourly until crisis is controlled.

30 minutes after the first dose of carbimazole: *LoE:III*[xliii]

- Lugol's iodine, oral, 10 drops in milk, 8 hourly.

AND

- ß–blocker, e.g.:
- Atenolol, oral, 50 mg daily
  - Titrate according to symptom control up to 100 mg daily.

If life-threatening:

ADD

- Hydrocortisone, IV, 100 mg 8 hourly.

Actively manage precipitating illness and infection. ICU admission is desirable.

REFFERRAL

All patients once stabilised.

References:

[i] ACTH, IM: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[ii]Hydrocortisone, IV: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

[iii] Sodium chloride 0.9%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Dextrose 50%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Sodium chloride 0.9%/ dextrose 5%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[iv] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[v] Fludrocortisone, oral: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[vi]Hydrocortisone, IV: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

[vii] Testosterone cypionate, IM: Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. https://www.ncbi.nlm.nih.gov/pubmed/20525906

Testosterone cypionate, IM: Pfizer, MCC registered package insert: Depo-testosterone™, 31 January 2016.

[viii] Dexamethasone, oral: Findling JW, Raff H, Aron DC. The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. J Clin Endocrinol Metab. 2004 Mar;89(3):1222-6. http://www.ncbi.nlm.nih.gov/pubmed/15001614

[ix] Diagnosis of diabetes mellitus: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Diagnosis of diabetes mellitus: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Review: HbA1c as a diagnostic test for diabetes, October 2017. http://www.health.gov.za/

Diagnosis of diabetes mellitus: Wheeler E, Leong A, Liu CT, et al. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. PLoS Med. 2017 Sep 12;14(9):e1002383. https://www.ncbi.nlm.nih.gov/pubmed/28898252

Diagnosis of diabetes mellitus: Herman WH, Ma Y, Uwaifo G, et al. Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457. https://www.ncbi.nlm.nih.gov/pubmed/17536077

[x] Monitoring of diabetes mellitus: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xi] Urine protein monitoring by dipstix: McFarlane P. Gilbert RE, MacCallum L, Senior P. Chronic Kidney Disease in Diabetes. Can J Diabetes 37 (2013) S129eS136.

Urine protein monitoring by dipstix: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Urine protein monitoring by dipstix: Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematic review. World J Diabetes. 2015 Jun 10;6(5):759-73. https://www.ncbi.nlm.nih.gov/pubmed/26069725

Urine protein monitoring by dipstix: MR Davids, N Marais, JC Jacobs. South African Renal Registry. Annual Report 2012. South African Renal Society, Cape Town 2014. http://sa-renalsociety.org/registry/

[xii] Metformin: Effect of intensive blood-glucose control with metformin on complications inoverweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group.Lancet. 1998 Sep

12;352(9131):854-65. Erratum in: Lancet1998 Nov 7;352(9139):1558.http://www.ncbi.nlm.nih.gov/pubmed/9742977

Metformin: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xiii] Metformin (renal impairment): Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212.
http://guidelines.diabetes.ca/app_themes/cdacpg/resources/cpg_2013_full_en.pdf

Metformin (renal impairment): The National Institute for Health and Care Excellence. Type 2 diabetes in adults: management Clinical Guideline, 2 December 2015. https://www.nice.org.uk/guidance/ng28

Metformin (renal impairment): Aronoff, Bennett et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th Edition. American College of Physicians.United States of America, 2007.

Metformin (renal impairment): Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7.
http://www.ncbi.nlm.nih.gov/pubmed/21617112

Metformin (renal impairment): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xiv] Glimepiride: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

[xv] Sulfonylureas: Niemi M, Backman JT, Neuvonen M, Neuvonen PJ, Kivistö KT. Effects of rifampin on the pharmacokinetics and pharmacodynamics of glyburide and glipizide. Clin Pharmacol Ther. 2001 Jun;69(6):400-6. https://www.ncbi.nlm.nih.gov/pubmed/11406737

[xvi] Insulin, biphasic, SC (starting dose): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xvii] Insulin therapy (Type 2 diabetes mellitus): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xviii] ACE-inhibitor:ACEI (ACE Inhibitors in Diabetic Nephropathy Trialist Group). Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin converting enzyme inhibitors? A meta-analysis of individual patient data. Annals of Internal Medicine 2001;134(5): 370–379.
http://www.ncbi.nlm.nih.gov/pubmed/11242497

[xix] Enalapril, oral (maximum daily dose of 40 mg): Joint Formulary Committee. British National Formulary. London: BMJ Group and Pharmaceutical Press; 2018.

[xx] Home blood glucose monitoring:Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH. et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med.2008;358(24):2545–2559.http://www.ncbi.nlm.nih.gov/pubmed/18539917

Home blood glucose monitoring:Östgren CJ, Sundström J, Svennblad B, Lohm L, Nilsson PM, Johansson G. Associations of HbA1c and educational level with risk of cardiovascular events in 32,871 drug-treated patients with Type 2 diabetes: a cohort study in primary care. Diabet Med. 2013 May;30(5):e170-7.
http://www.ncbi.nlm.nih.gov/pubmed/23350893

[xxi] Dextrose 50%, IV: Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. Emerg Med J. 2005 Jul;22(7):512-5.
https://www.ncbi.nlm.nih.gov/pubmed/15983093

Dextrose 50%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xxii] Dextrose 5%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Dextrose 5% in sodium chloride 0.9%, IV: The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[xxiii]Enoxaparin: Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):1476-86. http://www.ncbi.nlm.nih.gov/pubmed/17646601

[xxiv]HMGCoA reductase inhibitor (indications - CKD, albuminuria): Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, Cass A, Zhang H, Wang H. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013 Jun;34(24):1807-17. https://www.ncbi.nlm.nih.gov/pubmed/23470492

HMGCoA reductase inhibitor (indications - CKD, albuminuria): Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2017 Sep;33(6). https://www.ncbi.nlm.nih.gov/pubmed/28477396

[xxv] Simvastatin 40 mg, oral (secondary prevention of ischaemic events): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Simvastatin 40 mg, oral (secondary prevention of ischaemic events): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

[xxvi]Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. J Clin Transl Endocrinol. 2017 Feb 22;8:6-14. https://www.ncbi.nlm.nih.gov/pubmed/29067253

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): National Department of Health. Affordable Medicines, EDP-Primary Health Care. Cost-effectiveness analysis of high, intermediate, and low dose statins for the secondary prevention of cardiovascular disease, 31 January 2018. www.health.gov.za/

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. The Lancet 2010; 376(9753): 1670-81. https://www.ncbi.nlm.nih.gov/pubmed/21067804

Atorvastatin 10 mg, oral (secondary prevention of ischaemic events – patients on protease inhibitors): Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. European journal of preventive cardiology 2013; 20(4): 658-70. https://www.ncbi.nlm.nih.gov/pubmed/23529608

Atorvastatin, oral (drug-drug interaction with protease inhibitors): University of Liverpool. HIV drug interaction database. https://www.hiv-druginteractions.org/

[xxvii] Simvastatin 40 mg, oral (amlodipine drug interaction): Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7. https://www.ncbi.nlm.nih.gov/pubmed/16097365

Simvastatin 40 mg, oral (amlodipine drug interaction): Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8. https://www.ncbi.nlm.nih.gov/pubmed/23965645

[xxviii] High dose statins (management of adverse drug reactions): NICE: Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline, 18 July 2014. www.nice.org.uk/guidance/cg181

[xxix]Aspirin: DeBerardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009 Nov6;339:b4531.http://www.ncbi.nlm.nih.gov/pubmed/19897665

[xxx]Bisphosphonates, IV (therapeutic grouping): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Bisphosphonates, therapeutic class for hypercalcaemia, including primary hyperparathyroidism, September 2017. http://www.health.gov.za/

Bisphosphonates, IV (therapeutic grouping): Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, Broadley K. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess. 2004;8(4):1-176. https://www.ncbi.nlm.nih.gov/pubmed/14960258

Zoledronic acid, IV (dosing): The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

Zoledronic acid, IV (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[xxxi] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.

[xxxii] Calcium gluconate 10%, infusion (serum calcium <2 mmol/L): Tohme JF, Bilezikian JP. Diagnosis and treatment of hypocalcaemic emergencies. The Endocrinologist. 1996; 10-18.
http://journals.lww.com/theendocrinologist/Abstract/1996/01000/Diagnosis_and_Treatment_of_Hypocalcemic.3.aspx

[xxxiii]Hypothyroidism in pregnancy: Vadiveloo T, Mires GJ, Donnan PT, Leese GP. Thyroid testing in pregnant women with thyroid dysfunction in Tayside, Scotland: the thyroid epidemiology, audit and research study (TEARS). ClinEndocrinol (Oxf) 2013; 78:466.http://www.ncbi.nlm.nih.gov/pubmed/22548296

Hypothyroidism in pregnancy: Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J ClinEndocrinolMetab 2010; 95:3234.
http://www.ncbi.nlm.nih.gov/pubmed/20463094

Hypothyroidism in pregnancy: Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med. 2004 Jul 15;351(3):241-9.http://www.ncbi.nlm.nih.gov/pubmed/15254282

Hypothyroidism in pregnancy: Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002 Jan;12(1):63-8.

http://www.ncbi.nlm.nih.gov/pubmed/11838732
[xxxiv]Limited alcohol intake (osteoporosis): Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture. Osteoporos Int. 2005 Jul;16(7):737-42. https://www.ncbi.nlm.nih.gov/pubmed/15455194
[xxxv]Vitamin D, oral (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.
[xxxvi]Calcium: Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR. Calcium intake and risk of fracture: systematic review. BMJ. 2015 Sep 29;351:h4580. http://www.ncbi.nlm.nih.gov/pubmed/26420387
Vitamin D: Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR. Calcium intake and risk of fracture: systematic review. BMJ. 2015 Sep 29;351:h4580. http://www.ncbi.nlm.nih.gov/pubmed/26420387
[xxxvii]Bisphosphonates, oral (therapeutic class): Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess 2016;20(78). https://www.ncbi.nlm.nih.gov/pubmed/27801641
Bisphosphonates, oral (therapeutic class): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Bisphosphonates, oral therapeutic class for secondary prevention of fragility fractures, 31 October 2017. http://www.health.gov.za/
Bisphosphonates, oral (secondary prevention of steroid-induced bone loss): Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. Cochrane Database Syst Rev. 2016 Oct 5;10:CD001347. https://www.ncbi.nlm.nih.gov/pubmed/27706804
[xxxviii]Desmopressin, oral/IV/SC/nasal spray: Oiso Y, Robertson GL, Nørgaard JP, and Juul KV. Treatment of Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab 98: 3958–3967, 2013. https://www.ncbi.nlm.nih.gov/pubmed/23884783
Desmopressin, oral/IV/SC/nasal spray: British National Formulary, March 2017-September 2018. https://www.bnf.org/
[xxxix]Doxazosin: van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. Neth J Med. 2014 May;72(4):190-201. http://www.ncbi.nlm.nih.gov/pubmed/24829175
[xl]β-blockers (after adequate α-blockade): Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr, Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42.https://www.ncbi.nlm.nih.gov/pubmed/24893135
[xli] Atenolol, oral: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.
[xlii] Corticosteroids, oral (intermediate-acting therapeutic class): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology.University of Cape Town. 2016.
[xliii] Carbimazole: South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town. 2016.

Vvitam

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 8: ENDOCRINE DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 - 2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the endocrine chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
8.2 Adrenal insufficiency (Addison disease)		
- *Investigations*	ACTH depot, IM	Dose retained at "1 mg"
- *Severe stress*	Hydrocortisone, IV	Dose retained at "100 mg 6 hourly"
8.3 Androgen deficiency	Testosterone cypionate, IM	Dosing not amended; directions for use amended
8.5 Diabetes mellitus		
- *Diagnosis*	HbA1C	Not added for diagnosing diabetes mellitus
	Oral glucose tolerance test	Added
- *Monitoring*	Urine protein monitoring by dipstick	Baseline and annual monitoring added
	Serum lipids	Annual monitoring not added
8.5.1 Type 2 Diabetes mellitus	Glimepiride, oral	Maximum dose added
	Gliclazide, slow release oral	Not added
	Glucagon-like peptide 1 receptor agonist (GLP1 RA), oral	Not added
	Sodium glucose transporter 2(SGLT2) inhibitor, oral	Not added
	Dipeptidyl-peptidase-4 (DPP4) inhibitor, oral	Not added
	Pioglitazone, oral	Not added
8.5.1 Type 1 Diabetes mellitus	Long-acting insulin analogues	Not added
	Home glucose monitoring	Amended
8.6.1 Hypoglycaemia (In hospital)	Dextrose 50%, IV	Retained
	Glucagon, IM	Deleted
8.7.1 Diabetic neuropathies	Amitriptyline, oral	Deleted (Moved to pain chapter)
	Paracetamol, oral	Deleted (Moved to pain chapter)
	Carbamazepine, oral	Deleted (Moved to pain chapter)
8.8 Dyslipidaemia	HMGCoA reductase inhibitors	Indication extended to include CKD and microalbuminuria
- *Primary prevention of ischaemic events*	Simvastatin, oral	Dose retained as 10 mg
- *Secondary prevention of ischaemic events*	Simvastatin, oral	Dose amended from low 10 mg dose to intermediate 40 mg dose
- *Secondary prevention of ischaemic events: i) Drug-drug interaction with amlodipine*	Simvastatin, oral 10-20 mg	Added
- *Secondary prevention of ischaemic events: ii) Drug-drug interaction with protease inhibitors*	Atorvastatin, oral, 10 mg	Added
- *Secondary prevention of ischaemic events: iii) Managing ADRs associated with intermediate dose statins*	Simvastatin, oral, 10 mg	Added
- CVD risk assessment	Screening of IHD risk using BMI	Added
	Screening of IHD risk using Framingham tables	Retained
8.9 Hypercalcaemia, including primary hyperparathyroidism	Bisphosphonates, IV	Recommended as a therapeutic class; dose adjustment added for renal impairment
	Pamidronic acid, IV	Deleted from STG, as discontinued from market (but retained on therapeutic interchange database)
	Zoledronic acid, IV	Added as an example of therapeutic class – listed in STG

	Ibandronic acid, IV	Added as a therapeutic alternative
8.10 Hypocalcaemia	Calcium gluconate 10%, infusion	Dosing amended
8.12 Osteoporosis		
- Primary prevention	Vitamin D	Dose expanded
	Bisphosphonates, oral (class)	Indication of glucocorticoid-induced osteoporosis added
	Alendronic acid (example of class)	Indication of glucocorticoid-induced osteoporosis added
- Secondary prevention of osteoporotic fracture, including patients on long- term corticosteroids	Bisphosphonates, oral	Recommended as a therapeutic class
	Alendronic acid 70 mg, oral	Added as an example of therapeutic class – listed in STG
	Alendronic acid 10 mg, oral	Deleted as an example of therapeutic class in the STG, but added to therapeutic interchange database
	Risedronic acid 5 mg, oral	Added as a therapeutic alternative
	Risedronic acid 35 mg, oral	Added as a therapeutic alternative
	Zoledronic acid, IV	Not added as a therapeutic alternative
	Ibandronic acid, IV	Not added as a therapeutic alternative
8.14 Paget's disease	Urgent referral of neurological impairment for IV zoledronic acid	Not added
8.15.3 Diabetes insipidus (posterior hypopituitarism)	Desmopressin, oral	Directions for use amended
	Desmopressin, nasal spray	Directions for use amended
	Desmopressin, parenteral	Directions for use amended
8.18.1 Graves' hyperthyroidism	Beta-blockers, oral	Added as a therapeutic class
	Propranolol, oral	Added as a therapeutic alternative
	Atenolol, oral	Retained as the example of the beta-blocker group (listed in STG)
Gender dysphoria	Estradiol, oral	Not added (review for T&Q EML)
	Conjugated estrogens, oral	Not added (review for T&Q EML)
	Spironolactone, oral	Not added (review for T&Q EML)
	Testosterone cypionate, IM	Not added (review for T&Q EML)
	Medroxyprogesterone, IM	Not added (review for T&Q EML)
8.18.4 Thyroiditis	Beta-blockers, oral	Added as a therapeutic class
	Propranolol, oral	Added as a therapeutic alternative
	Atenolol, oral	Retained as the example of the beta-blocker group (listed in STG)
8.18.5 Thyroid crisis	Beta-blockers, oral	Added as a therapeutic class
	Propranolol, oral	Added as a therapeutic alternative
	Atenolol, oral	Retained as the example of the beta-blocker group (listed in STG)

8.2 ADRENAL INSUFFICIENCY (ADDISON DISEASE)

Investigations

ACTH depot, IM: *dose retained at "1 mg"*

The 1mg/ml preparation is readily available, whilst the 250 mcg preparation is only available on a named-patient basis with permission from the South African Health Products Regulatory Authority.

Level of Evidence: III Guidelines[1]

During times of severe "stress" i.e. acute illness, surgery, trauma, etc.:

Hydrocortisone, IV: *dose retained at "100 mg 6 hourly"*

Aligned with the European Society of Endocrinology Guidelines[2], that recommends "*Hydrocortisone 100 mg iv immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day".* The Society acknowledged paucity of RCT evidence investigating corticosteroid dosing in patient with adrenal insufficiency during times of increased cortisol need, and severity and duration of the stressor

[1] SAMF, 2016

[2] Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/26760044

usually determines the dose. The Guideline recommendation placed a higher value on prevention of adrenal crisis than on reducing the potential negative effect of short-term overtreatment. The recommendation in the STG is an adaptation of the European Society of Endocrinology Guidelines, adapted for pragmatic purposes.
Level of Evidence: III Guidelines

8.3 ANDROGEN DEFICIENCY

Testosterone cypionate, IM: *dosing not amended; directions for use amended*
Dose: Aligned with MCC registered package insert for management of eunuchoidism. The dose of 100-200 mg every 3-6 weeks is recommended for treatment of oligosperma that is not managed at secondary level of care.
Approved package insert for testosterone cypionate[3] recommends:

- 200 – 400mg injected every 3-4 weeks for eunuchoidism
- 100 – 200mg every 3-6 weeks for oligospermia.

Level of Evidence: III Package insert, Expert opinion

Directions for use: Guidance provided that testosterone therapy be stopped, if haematocrit exceeds 54%. Meta-analysis[4] (studies of low to medium methodological quality) showed that testosterone treatment was associated with a significant increase in haemoglobin: weighted mean difference (WMD), 0.80 g/dl; 95% CI 0.45 to 1.14; and haematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). No significant effect on mortality, prostate, or cardiovascular outcomes.
Level of Evidence: I Meta-analysis

8.5 DIABETES MELLITUS

Diagnosis
HbA1C: *not added for diagnosing diabetes mellitus*
Refer to the October 2017 evidence summary: Should HbA1C be used as a diagnostic test for diabetes mellitus?

HbA1C for Diagnosising DM_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Evidence is inconclusive regarding the race/ethnic influence on HbA1C. The test has not been validated in the South African population to diagnose diabetes and is more expensive than the current standard finger prick glucose test.
Level of Evidence: III Human genetic studies, Prevalence study, Guidelines

Oral glucose tolerance test: *added*
The 2-hour plasma glucose in a 75g oral glucose tolerance test ≥ 11.1 mmol/l was added as an option to diagnose diabetes mellitus, aligned with guidelines.
Level of Evidence: III Guidelines[5]

Monitoring:
Urine protein monitoring by dipstick: *baseline and annual monitoring added*
Recent studies have made it clear that both kidney function (eGFR) and albuminuria are independent risk factors for progression to kidney failure[6]. Both are required to diagnose and monitor diabetic kidney disease. Albuminuria is

[3] Pfizer, MCC registered package insert: Depo-testosterone™, 31 January 2016.
[4] Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. https://www.ncbi.nlm.nih.gov/pubmed/20525906
[5] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[6] Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883.

often detected long before the eGFR drops, thus allowing for earlier CKD diagnosis and intervention[7]. Diabetic kidney disease may classically progress form subclinical disease to the earliest clinical detectable stage, characterized by persistent proteinuria[8].
PHC 2014 STG recommends routine screening for microalbuminuria. Despite a Cochrane review[9] suggesting that ACE-inhibitors reduce the risk of new onset moderate and severe albuminuria, PHC STGs and EML[10] recommends screening rather than routine administration of an ACE inhibitor to every diabetic at primary level; as prevalence of diabetics with microalbuminuria is low[11] [12]. The PHC STGs and EML and the current Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines[13] recommends annual screening, except patients already on an ACE Inhibitor in order to minimise wasteful expenditure.
Monitoring for urine protein by dipstick was aligned with the PHC STGs and EML, for consistency and correctness.
Level of Evidence: III Guidelines

Serum lipids: *annual monitoring not added*
Despite annual screening of lipids being standard of care as per guidelines[14], the current local public healthcare approach is a "fire and forget" approach, as the "treat to target" approach is too expensive. Intervention of an increased dose of statin following a laboratory result of increased serum lipids is currently not recommended in the STGs.
Level of Evidence: III Expert opinion

8.5.1 TYPE 2 DIABETES MELLITUS

Glimepiride, oral: *maximum dose added*
Maximum dose of 8 mg per day was added to the text of the STG, aligned with the SAMF 2016; though the approximate equivalent dose of glimepiride to gliclazide is 2:160 mg.
Level of Evidence: III Guidelines[15]

Gliclazide, slow release oral: *not added*
Glucagon-like peptide 1 receptor agonist (GLP1 RA), oral: *not added*
Sodium glucose transporter 2(SGLT2) inhibitor, oral: *not added*
Dipeptidyl-peptidase-4 (DPP4) inhibitor, oral: *not added*
Pioglitazone, oral: *not added*

The NEMLC had previously recommended glimepiride or glibenclamide as the sulfonylureas of choice, as gliclazide was considered to be comparable to glimepiride. Gliclazide (both the immediate- and slow release formulations) considered to be expensive. The other oral agents listed above to be considered for review by the Tertiary & Quaternary Committee.

Metformin, oral: *dose amended in renal impairment*
Aligned with the SEMDSA Type 2 Diabetes Guidelines Expert Committee Clinical Practice Guidelines, 2017.
Level of Evidence: III Guidelines[16]

[7] Levey AS, Becker C, Inker LA.Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review.JAMA. 2015 Feb 24;313(8):837-46.
[8] McFarlane P. Gilbert RE, MacCallum L, Senior P. Chronic Kidney Disease in Diabetes. Can J Diabetes 37 (2013) S129eS136.
[9] Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2012Dec 12;12:CD004136.
[10] National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2018. http://www.health.gov.za/
[11] Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: A systematicreview. World J Diabetes. 2015 Jun 10;6(5):759-73.
[12] MR Davids, N Marais, JC Jacobs. South African Renal Registry. Annual Report2012. South African Renal Society, Cape Town 2014.
[13] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[14] Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care. 2017 Jan;40(Suppl 1):S4-S5.
[15] SAMF, 2016
[16] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.
http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

8.5.1 TYPE 1 DIABETES MELLITUS

Long-acting insulin analogues: *not added*
External comment was received to consider insulin analogues; for review by the Tertiary & Quaternary Committee at tertiary/quaternary level of care.

Home glucose monitoring: *amended*
Frequency of monitoring for patients on basal/bolus insulin was amended from "at least once daily" to "3-4 times a day" for correctness.
Level of Evidence: III Expert opinion

8.6.1 HYPOGLYCAEMIA

In hospital
Dextrose 50%, IV: *retained*
Glucagon, IM: *deleted*

Dextrose 50%, IV: An external comment was received motivating for lower concentrations of dextrose as 50% was reported to cause extravasation. However, there is a paucity of evidence of extravasation injuries associated with 50% dextrose, IV[17]. The current recommendation for administering dextrose 50%, IV for hypoglycaemia was retained; as this was considered appropriate for the clinical setting at secondary level of care, and is aligned with 2017 SEMDSA guidelines[18].
Level of care: III Guidelines, Expert opinion

Glucagon, IM: A systematic review and meta-analysis by Boido et al (2015)[19] showed that in comparison to IV dextrose, glucagon had frequent reports of being inefficacious; OR 0.53 (95% CI 0.20 to 1.42) favouring the use of dextrose. The authors concluded that a second dose should be administered if no other remedies are available and if the patient does not respond within 15 minutes. Furthermore, if glycogen levels are depleted as might be the case in severe starvation, adrenal insufficiency or alcoholic hypoglycaemia, glucagon might not be effective in raising blood glucose levels.
Recommendation: Glucagon, IM deleted from the EML for management of hypoglycaemia at secondary level of care.
Rationale: A systematic review and meta-analysis showed that in comparison to IV dextrose, glucagon had frequent reports of being inefficacious; OR 0.53 (95% CI 0.20 to 1.42) favouring the use of dextrose. Dextrose, IV is readily accessible at district hospitals.
Level of evidence: I Systematic review, Guidelines

8.7.1 DIABETIC NEUROPATHIES

Amitriptyline, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*
Paracetamol, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*
Carbamazepine, oral: *deleted with a cross-reference to section 26.1.4 Management of neuropathic pain*

8.8 DYSLIPIDAEMIA

HMGCoA reductase inhibitors: *indication extended to include CKD and microalbuminuria*

[17] Moore C, Woollard M. Dextrose 10% or 50% in the treatment of hypoglycaemia out of hospital? A randomised controlled trial. Emerg Med J. 2005 Jul;22(7):512-5.
[18] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937
[19] Boido A, Ceriani V, Pontiroli AE. Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: a systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. Acta Diabetol. 2015 Apr;52(2):405-12. https://www.ncbi.nlm.nih.gov/pubmed/25323325

Guidelines: South African heart association and the lipid and atherosclerosis society of Southern Africa (LASSA) guidelines[20] recommend starting statins in all patients with CKD and type 1 diabetics with microalbuminuria or proteinuria.
Hou et al[21]: A systematic review looking at statin therapy in CKD patients (eGFR<60 ml/min/1.73 m^2) found that major cardiovascular events were reduced by 23%, including a 22% reduction in coronary events, and 9% reduction in cardiovascular or all-cause death. Although the most benefit is seen in patients with earlier stages of CKD, there was modest benefit in dialysis/non-dialysis stage 5 patients too. A subgroup analysis of 3 trials with >40% diabetics, showed a similar statistically significant benefit of 17% when using statins in CKD.
Qin et al[22]: Systematic review and meta-analysis al looking at the effects of statins on renal outcomes in patients with diabetic kidney disease, found that statins have beneficial effects on reducing albuminuria in diabetic kidney disease patients. However, there was no evidence that the same intervention had an effect on overt proteinuria or eGFR outcomes in these patients.
PHC STGs and EML: Further aligned with most recent NEMLC approved PHC STGs and EML[23] recommendation.

Recommendation: Indication for HMGCoA reductase inhibitors extended to include CKD and microalbuminuria.
Rationale: Available evidence suggests that statins are beneficial in reducing major cardiovascular events, coronary events, cardiovascular or all-cause death in patients with CKD. However, statins were shown to reduce albuminuria and not overt proteinuria or eGFR, in diabetic kidney disease patients
Level of Evidence: I Systematic reviews

Alignment with NEMLC-approved PHC STGs and EML
Recommendations aligned with most recent NEMLC approved PHC STGs and EML, 2018[24] recommendation.
Refer to the PHC Cardiovascular NEMLC report (2016-2018), published on the National Department of Heath website for detailed information (indications, dosing, drug-drug interactions, side-effects, members of therapeutic groups). Available at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/497-national-essential-medicine-list-committee-nemlc

PHC_Cardiovascular_NEMLC report_201(

Myalgia
The Adult Hospital Level STGs and EML, 2019 recommends that if myalgia develops whilst on a statin, then to reduce the dose to simvastatin 10 mg or equivalent. The Adult Hospital Level Committee recommends that provision be made for 20 mg simvastatin or equivalent and that this be listed on the therapeutic interchange database.

Drug interaction of statins with amlodipine
Simvastatin, oral (or equivalent): *dose amended from "10 mg" to "10-20 mg"*

Background: An external comment was received about the use of a dose higher than simvastatin 10 mg with concomitant amlodipine.

Review: Simvastatin is metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) and is a substrate of CYP3A4. Amlodipine is a weak inhibitor of CYP3A4, with simvastatin being susceptible to the inhibitory effect of amlodipine. Amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin.[25] Concomitant administration of amlodipine with simvastatin could lead to a greater risk of adverse effects such as myopathy and

[20] South African heart association and the lipid and atherosclerosis society of Southern Africa (LASSA). South African dyslipidaemia guideline consensus statement. S Afr Med J 2012;102:177-188.
[21] Hou W,et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013 Jun;34(24):1807-17. https://www.ncbi.nlm.nih.gov/pubmed/23470492
[22] Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2017 Sep;33(6). https://www.ncbi.nlm.nih.gov/pubmed/28477396
[23] Minutes of the NEMLC meetings of 1 February 2018 and 12 April 2018.
[24] Minutes of the NEMLC meetings of 1 February 2018 and 12 April 2018.
[25] Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7.

rhabdomyolysis. A dose of maximum 20 mg simvastatin together with amlodipine 10 mg, has been found to be safe and effective.[26] A dose exceeding 20 mg simvastatin in combination with 10 mg amlodipine is not recommended.
Atorvastatin, a substrate of CYP3A4, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine. The dose of atorvastatin is not to exceed 80 mg with concomitant administration of amlodipine 10 mg.[27]

Recommendation: Reduced dose of simvastatin 10 to 20 mg be recommended for patients on concomitant amlodipine.
Rationale: Drug-drug interaction of simvastatin with amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin with possible subsequent myopathy and rhabdomyolysis. Pharmacokinetic studies suggests that maximum dose of simvastatin 20 mg is safe when used in combination with amlodipine 10 mg. Atorvastatin, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine and thus, atorvastatin 20 mg is recommended for use with concomitant amlodipine.
Level of Evidence: III Pharmacokinetic studies, Guidelines

Indication/Assessment	Recommendation
Primary prevention of ischaemic events	Simvastatin, oral: *dose retained as 10 mg*
Secondary prevention of ischaemic events	Simvastatin, oral: *dose amended from low 10 mg dose to intermediate 40 mg dose*
Secondary prevention of ischaemic events: **i) Drug-drug interaction with amlodipine**	Simvastatin, oral: *10-20 mg added*
Secondary prevention of ischaemic events: **ii) Drug-drug interaction with protease inhibitors**	Atorvastatin, oral: *10 mg added*
Secondary prevention of ischaemic events: **iii) Managing ADRs associated with intermediate dose statins**	e.g. Simvastatin, oral: *10-20 mg added*
Cardiovascular disease risk assessment	Screening of IHD risk using BMI: *added* Screening of IHD risk using Framingham tables: *retained*

8.9 HYPERCALCAEMIA, INCLUDING PRIMARY HYPERPARATHYROIDISM

Bisphosphonates, IV: *recommended as a therapeutic class and dose adjustment added for renal impairment*
Pamidronic acid, IV: *deleted from STG, as discontinued from market (but retained on therapeutic interchange database)*
Zoledronic acid, IV: *added as an example of therapeutic class – listed in STG*
Ibandronic acid, IV: *added as a therapeutic alternative*
Background: Previously, pamidronic acid, IV was recommended for hypercalcaemia, including primary hyperparathyroidism in the Adult Hospital Level STGs and EML, 205 edition. However, this medicine has been discontinued form the South African market. The Adult Hospital Level Committee reviewed the evidence for consideration of bisphosphonates, IV as a therapeutic class in this clinical setting.

Refer to the medicine review, bisphosphonates for hypercalcaemia (September 2017):

Bispohsphonates for Hypercalcaemia_

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the effectiveness of bisphosphonates therapy for hypercalcaemia and the discontinuation of the pamidronic acid in South Africa, alternative bisphosphonate therapy was required. Zoledronic 4mg, IV and ibandronic 2-4 mg, IV were options that could be considered. Zoledronic acid was the cheapest agent to be listed as the example of class in the STG. The NEMLC recommended the Adult Hospital Level Committee review the evidence

[26] Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8.
[27] SAMF, 2016/2020

for a lower dose of zoledronic acid, possibly to 2 mg. However, no available RCT evidence or guideline recommendations could be sourced for low dose zoledronic acid, IV in this clinical setting. However, dose adjustments are recommended in real impairment and zoledronic acid, IV is contra-indicated when eGFR < 35ml/min.

Rationale: Evidence of comparable effectiveness of bisphosphonates (pamidronic acid, zoledronic acid and ibandronic acid).

Level of Evidence: II Systematic review of low quality RCTs[28] [29], III Guidelines[30] [31]

Text of the STG was updated to:

- Bisphosphonates, e.g.:
- Zoledronic acid, IV infusion, 4 mg over 15 minutes (specialist initiated).
  - eGFR 35 to 60 ml/min, adjust dose in consultation with specialist.

Note: Do not use if eGFR < 35 ml/min.

8.10 HYPOCALCAEMIA

For acute hypocalcaemia with neurological problems

Calcium gluconate, infusion: *dosing amended*

Guidelines[32] recommends administration of calcium in hypocalcaemia where serum calcium <2 mmol/L, as calcium gluconate 10% 20ml in 100ml dextrose 5% over 20 minutes with ECG monitoring as initial management to raise calcium for 1-2 hours, followed with an infusion of 15mg elemental calcium/kg body weight over 4-6 hours (10ml 10% Ca gluconate contains 90mg elemental calcium i.e. 9mg/ml).

The STG was updated as follows:

- Calcium gluconate 10%, infusion, 20 mL in 100 mL dextrose 5% given over 20 minutes, with ECG monitoring.

AND

- Calcium gluconate 10%, infusion, 15 mg/kg (= wt [kg] x1.7mL) in 1000 mL sodium chloride 0.9% over 4 hours.

Level of Evidence: III Guidelines

8.12 OSTEOPOROSIS

Primary prevention

Vitamin D: *dose expanded*

Dose expanded to include daily (800 units) and weekly dosing (50 000 units), as suggested by SAMF, 2016.

Level of Evidence: III Guidelines[33]

Glucocorticosteroid-induced osteoporosis (GIOP)

Bisphosphonates, oral (class): *indication of glucocorticoid-induced osteoporosis added*

Alendronic acid (example of class): *indication of glucocorticoid-induced osteoporosis added*

Background: During the final clinical editing process of the Adult Hospital Level STGs and EML, 2019 edition, guidance for glucocorticosteroid-induced osteoporosis (GIOP) was included in section 13.6 Systemic lupus erythematosus (SLE) as below (accepted by NEMLC electronically):

[28] Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, Broadley K. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess. 2004;8(4):1-176. https://www.ncbi.nlm.nih.gov/pubmed/14960258

[29] Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol. 2001 Jan 15;19(2):558-67. https://www.ncbi.nlm.nih.gov/pubmed/11208851

[30] SAMF, 2016

[31] The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196. http://www.jemdsa.co.za/index.php/JEMDSA/article/view/647/937

[32] Tohme JF, Bilezikian JP. Diagnosis and treatment of hypocalcaemic emergencies. The Endocrinologist. 1996; 10-18.

[33] SAMF, 2016

Patients requiring corticosteroids for >3 months (long-term) should be managed for secondary prevention of osteoporotic fractures. See section 8.12: Osteoporosis.

Level of Evidence: I Systematic review and meta-analysis

Query: However, section 8.12 does not provide sufficient guidance for GIOP, and this has created confusion amongst end-users of this guideline. Query had been received from George, Western Cape.

Glucocorticoid-induced osteoporosis: Corticosteroids (immunosuppressants) are widely used in inflammatory conditions, but bone-loss and GIOP is a serious adverse drug reaction associated with chronic corticosteroids[2].

Evidence: Cochrane review[34] of 12 RCTs (n=1343) showed that amongst adults taking chronic corticosteroids (mean steroid dose ≥5.0 mg/day), 2% fewer (95% CI 5% fewer to 1% more) sustained incident vertebral fractures with bisphosphonates vs. no bisphosphonates, followed up over a period of 24 months (high-certainty evidence); RR 0.57 (95% CI 0.35 to 0.91), I^2=0%; NNTB 31 (95%CI 21 to 145).

Low-certainty evidence suggested that bisphosphonates may make little or no difference in preventing non-vertebral fractures; RR 0.79 (95% CI 0.47 to 1.33), I^2=0%. Whilst moderate-certainty evidence showed that bisphosphonates are beneficial in preventing and treating corticosteroid-induced bone loss at both the lumbar spine and femoral neck; Mean difference 3.5 (95% CI 2.9 to 4.1), I^2=69.93%.

Low-certainty evidence showed that bisphosphonates may be associated with a low number serious adverse events or withdrawals due to adverse events; however, the authors cautioned about the possible risk of bias. Rare serious adverse events associated with bisphosphonates includes osteonecrosis of the jaw and atypical femur fractures[35].

Authors concluded that the use of bisphosphonates reduces the risk of vertebral fractures and the prevention and treatment of steroid-induced bone loss. The main limitation of this meta-analysis was the heterogeneity between RCTs (possibly due to different patient characteristics, underlying inflammatory conditions, steroid doses, and prevalent fractures and reported outcomes).

Study participants in the Cochrane review: Adults (>18 years) with underlying inflammatory disorders, initiating treatment or currently being treated with systemic corticosteroids, and who had not received bisphosphonates in the six months prior to the start of the study. In GIOP literature, the concept of rapid bone loss within the first three to six months of corticosteroid use is described.[36] [37]

Steroid dose and duration in the Cochrane review: RCTs included in the review had a mean corticosteroid dose of ≥5 mg/day (e.g. prednisone, oral), and participants were on therapy throughout the duration of the study. Study periods varied from 12 to 48 months. RCTs of patients on transplant-associated steroid use were excluded from the review.

Concomitant medicine in the Cochrane review: RCTs evaluated bisphosphonates with or without calcium and/or vitamin D as the active treatment arm; whilst the comparators included calcium and/or vitamin D or placebo.

Guidance for primary prevention of osteoporosis was expanded in the STG to adequately describe guidance for GIOP, as follows:

Primary prevention:
For glucorticoid-induced osteoporosis, i.e. patient on long-term (>3 months) corticosteroids at doses ≥5 mg/day
- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

Secondary prevention of osteoporotic fracture~~, including patients on long- term corticosteroids:~~
In severe osteoporosis, i.e. patients who have a T-score of –2.5 (severe osteoporosis) plus an osteoporotic fracture.
- Bisphosphonates, e.g.:
- Alendronic acid, oral, 70 mg weekly, for a maximum duration of 5 years.
  - Taken with a full glass of water, 30 minutes before breakfast – do not lie down.

[34] Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev*. 2016;10(10):CD001347. https://pubmed.ncbi.nlm.nih.gov/27706804/
[35] SAMF, 2016
[36] Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319-1328. https://pubmed.ncbi.nlm.nih.gov/17566815/
[37] van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002;13(10):777-787. https://pubmed.ncbi.nlm.nih.gov/12378366/

Supplement bisphosphonate therapy with:

- Calcium, elemental, oral, 1 000mg daily.

AND

- Vitamin D (Calciferol), oral, 800 units daily.

Level of Evidence: I Meta-analysis

Secondary prevention of osteoporotic fracture, including patients on long-term corticosteroids

Bisphosphonates, oral: *recommended as a therapeutic class*
Alendronic acid 70 mg, oral (weekly dose): *added as an example of therapeutic class – listed in STG*
Alendronic acid 10 mg, oral (daily dose): *deleted as an example of therapeutic class in the STG, but added to therapeutic interchange database*
Risedronic acid 5 mg, oral (daily dose): *added as a therapeutic alternative*
Risedronic acid 35 mg, oral (weekly dose): *added as a therapeutic alternative*
Zoledronic acid, IV: *not added as a therapeutic alternative*
Ibandronic acid, IV: *not added as a therapeutic alternative*

Refer to the medicine review, bisphosphonates for osteoporosis (October 2017):

Bisphosphonates for Osteoporosis_Ac

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review on the effectiveness of bisphosphonates therapy for preventing fragility fractures, oral bisphosphonates were recommended as a therapeutic class on the secondary level EML (i.e. alendronic acid 70 mg, risedronic acid 35 mg, alendronic acid 10 mg and risedronic acid 5 mg - the least expensive agent, alendronic acid 10 mg daily is preferred, but the other oral agents may be considered where there are supply chain issues).

Rationale: Clinically all bisphosphonates reduced the risk of vertebral fractures compared with no treatment. No bisphosphonate was found to be superior to any other at preventing fractures. All treatments were associated with beneficial effects relative to placebo.
Pairwise comparisons between treatments indicated that no active treatment was statistically significantly more effective than any other active treatment for fracture outcomes. For vertebral fractures and percentage change in femoral neck BMD, the greatest effect was for zoledronic acid, although in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects. There was no evidence to suggest different treatment effects according to age or sex. Oral bisphosphonates have similar rates of gastrointestinal toxicity when compared with placebo; whilst Intravenous bisphosphonates, especially zoledronic acid, are more likely to predispose patients to osteonecrosis of the jaw.
The de novo economic model from the systematic review suggests that the cost-effectiveness of IV bisphosphonates (ibandronic acid and zoledronic acid) is less favourable than for oral bisphosphonates with a negative incremental net benefit compared to no treatment; estimated for both IV bisphosphonates across all 10 risk categories for both FRAX and QFracture.
Level of Evidence: I Health Technology Assessment[38]

8.14 PAGET'S DISEASE

Referral

Urgent referral of neurological complications: *not added*
External comment to refer neurological complications for IV zoledronic acid was not considered, as there is a paucity of RCT evidence that zoledronic acid, IV prevents/improves long-term neurological impairment. Despite, limited evidence

[38] Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess 2016;20(78). https://www.ncbi.nlm.nih.gov/pubmed/27801641

showing that zoledronic IV improves bone pain and quality of life; all patients are referred for management at tertiary level of care.

8.15.3 DIABETES INSIPIDUS (POSTERIOR HYPOPITUITARISM)

Desmopressin, oral: *directions for use amended*
Desmopressin, nasal spray: *directions for use amended*
Desmopressin, parenteral: *directions for use amended*

Guidance for the management of diabetes insipidus with desmopressin was updated as follows, aligned with expert opinion[39] [40]:

Postoperative or acutely ill patients:

- Desmopressin, IV/SC, 2–4 mcg daily, either as a single dose or in 2 divided doses.

OR

Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.

OR

Desmopressin, oral, 0.05 mg, 8–12 hourly.

- Optimal dose: 0.1–0.8 mg daily.
- Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

If patient has a normal thirst mechanism, and does not receive IV fluids for other purposes:

» oral, intranasal, or IV/SC dosing can be used; and
» keep urine osmolality at 450–600 mOsm/kg.

If patient requires IV fluids and/or is unable to regulate total fluid intake by thirst mechanism:

» IV dosing is preferred; and
» continually adjust the level of antidiuresis to maintain hydration and plasma sodium within the normal.

Replacement therapy:

- Desmopressin, nasal spray, 10–40 mcg daily, either as a single dose or in 2–3 divided doses.
  - Adjust morning and evening doses separately for appropriate diurnal rhythm of water turnover.

OR

Desmopressin, oral, 0.05 mg, either as a single dose or in 2–3 divided doses.

- Optimal dose: 0.1–0.8 mg daily.
- Adjust dose according to response to a maximum of 1.2 mg daily in divided doses.

Level of Evidence: III Expert opinion

8.18.1 GRAVES' HYPERTHYROIDISM

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group (listed in STG)*

Previously, it was recommended that propranolol not be recommended for management of Graves' hyperthyroidism due to possible concerns of associated heart failure[41] and the advantage of daily dosing of atenolol as opposed to 8 hourly dosing of propranolol. However, this is currently standard of care and extensively used in clinical practice.
Level of Evidence: III Pharmacokinetic studies, Expert opinion

[39] Oiso Y, Robertson GL, Nørgaard JP, and Juul KV. Treatment of Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab 98: 3958–3967, 2013.
[40] British National Formulary, September 2017-March 2018 edition.
[41] SAMF, 2016

Beta-blocker, oral therapeutic group for hyperthyroidism			
Medicine	*Daily dose*	*Level of evidence*	*Price of daily dose*[42]
Atenolol, oral	100 mg daily	**Level of evidence: III** **Pharmacokinetic studies**[43] [44]**,** **Expert opinion**[45]	R 0.15
Propranolol, oral	40-80 mg 8 hourly		R 0.22 to R 0.44

GENDER DYSPHORIA

Estradiol, oral: *not added*
Conjugated estrogens, oral: *not added*
Spironolactone, oral: *not added*
Testosterone cypionate, IM: *not added*
Medroxyprogesterone, IM: *not added*

Motivation initially submitted to PHC Committee, and deliberations were made regarding management of this condition at secondary level of care or rather specialised treatment at tertiary level of care with down-referral.
The Adult Hospital Level Committee recognised the importance of managing gender dysphoria but was of the opinion that expertise is required within a specialised unit.
Recommendation: The motivation be reviewed by the Tertiary and Quaternary Committee for consideration.

8.18.4 THYROIDITIS

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group*
Aligned with section 8.18.1: Graves' hyperthyroidism.

8.18.5 THYROID CRISIS

Beta-blockers, oral: *added as a therapeutic class*
Propranolol, oral: *added as a therapeutic alternative*
Atenolol, oral: *retained as the example of the beta-blocker group*
Aligned with section 8.18.1: Graves' hyperthyroidism.

2024 updates following the publication of chapter

An external query received in May 2024, regarding the NEMLC STG recommendation of vitamin D supplementation as either 800 IU daily or calciferol 50 000 IU weekly for the primary prevention of osteoporosis was reviewed by NEMLC.

[42] Contract circular RT289-2019: Average weighted price of 40mg propranolol = R0.222; Atenolol 100mg tabs, 28 = R4.15.
[43] Perrild H, Hansen JM, Skovsted L, Christensen LK. Different effects of propranolol, alprenolol, sotalol, atenolol and metoprolol on serum T3 and serum rT3 in hyperthyroidism. Clin Endocrinol (Oxf). 1983 Feb;18(2):139-42. https://www.ncbi.nlm.nih.gov/pubmed/6133659
[44] Wilkins MR, Franklyn JA, Woods KL, Kendall MJ. Effect of propranolol on thyroid homeostasis of healthy volunteers. Postgrad Med J. 1985 May;61(715):391-4. https://www.ncbi.nlm.nih.gov/pubmed/3927277
[45] Geffner DL, Hershman JM. Beta-adrenergic blockade for the treatment of hyperthyroidism. Am J Med. 1992 Jul;93(1):61-8. https://www.ncbi.nlm.nih.gov/pubmed/1352658

NEMLC considered the associated risk of falls associated with high dose intermittent vitamin D supplementation in the prevention of fractures[46]-[47]. An erratum correcting the dose of vitamin D (Calciferol) (ref:2024/05/08/EDP/01) FROM 50 000 IU weekly to 50 000 IU every 4 weeks was published. It is recommended for long term supplementary Vitamin D (Calciferol) dosing to not exceed 50 000 IU every second week. The STG has been amended as follows:

MEDICINE TREATMENT

Primary prevention

In institutionalised frail elderly patients, supplementation with calcium and vitamin D may reduce the incidence of hip fractures:

- Calcium, elemental, oral, 1 000 mg daily.

AND

Vitamin D (Calciferol), oral, 800 units daily **or** ~~50 000 units weekly~~ 50 000 IU every 4 weeks.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note**: Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[46] Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010 May 12;303(18):1815-22. doi: 10.1001/jama.2010.594. Erratum in: JAMA. 2010 Jun 16;303(23):2357. PMID: 20460620.

[47] Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA internal medicine. 2016 Feb 1;176(2):175-83.