MIL

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Management of Hypercalcaemia of Unknown Origin

Serum calcium concentration is tightly regulated under physiological conditions. If there are abnormalities of parathyroid function, bone resorption, renal calcium reabsorption or dihydroxylation of vitamin D, then homeostasis may not be maintained and serum calcium may rise.[1] 50% of serum calcium is bound or complexed, largely to albumin.[2] Only the free calcium is physiologically active, therefore the reported "adjusted" or "corrected" calcium value should be used when interpreting levels.

Severity of Hypercalcaemia

Mild Below 3.0mmol/L	Often asymptomatic and does not usually require urgent correction.[1]
Moderate 3.0-3.5mmol/L	May be well tolerated if it has risen slowly but may be symptomatic and prompt treatment is usually indicated.[1]
Severe Over 3.5mmol/L	Requires urgent correction due to the risk of dysrhythmia and coma.[1]

Patients with severe hypercalcaemia or severe symptoms should be admitted to hospital. In patients with mild or moderate hypercalcaemia, consider repeating serum calcium concentration after 1 week.[3]

Symptoms [1, 3]

Skeletal: bone pain and fractures.

Neuromuscular: drowsiness, delirium, coma, fatigue, muscle weakness, impaired concentration and memory, depression, mood disturbance and neurological signs (e.g. ataxia).

Gastrointestinal: nausea, vomiting, anorexia, weight loss, constipation, abdominal pain, peptic ulcer and pancreatitis.

Renal: polyuria, polydipsia, dehydration, renal colic (due to nephrolithiasis) and renal impairment (due to nephrocalcinosis).

Cardiovascular: hypertension, shortened QT interval, cardiomyopathy and dysrhythmias.

Other: itching, keratitis, conjunctivitis and corneal calcification.

The extent of symptoms relates to the severity and rate of onset of hypercalcaemia. However, many people with chronic hypercalcaemia are asymptomatic, particularly in mild cases.

Initial Investigations [1, 3]

History

- Symptoms of hypercalcaemia and duration
- Symptoms of underlying causes e.g. weight loss, night sweats, cough
- Family history
- Drugs including supplements and over-the-counter preparations

Examination

- Assess for cognitive impairment
- Fluid balance status
- Assess for underlying causes including neck, respiratory, abdomen, breasts, lymph nodes

ECG

- Look for shortened QT interval or other conduction abnormalities

Bloods

– Calcium adjusted for albumin
– Phosphate
– Magnesium
– Parathyroid hormone (PTH)
– Urea and electrolytes
– 25(OH) vitamin D
– Consider erythrocyte sedimentation rate (ESR) and paraproteins

Avoid prolonged application of tourniquet during venepuncture as this may lead to increased apparent serum calcium concentration.

High calcium and high PTH = primary or tertiary hyperparathyroidism (rarely Familial Hypocalciuric Hypercalcaemia, FHH).[1]

High calcium and low PTH = malignancy or other rarer causes.[1]

Over 90% of hypercalcaemia is caused by malignancy or primary hyperparathyroidism.[2]

Management of severe or symptomatic hypercalcaemia [1, 3]

Please also refer to Management of hypercalcaemia of malignancy MIL if appropriate.

1. Rehydration

Intravenous 0.9% saline 4-6 litres in 24h

– Monitor for fluid overload if **renal** or **cardiac** impairment or elderly
– Loop diuretics rarely used and only if fluid overload develops; not effective for reducing serum calcium
– May need to consider dialysis if severe renal failure

2. Bisphosphonates (after rehydration)

Zoledronic acid 4mg intravenously over 15 mins or **Disodium pamidronate** 30mg to 90mg (depending on severity of hypercalcaemia) as an intravenous infusion at 20mg/hour.[4, 5]

– Give more slowly and consider dose reduction in renal impairment. Contact Pharmacy for advice on dosing in renal impairment.
– Monitor serum calcium response, will reach nadir at 2 to 4 days
– Can cause hypocalcaemia if vitamin D deficiency or suppressed PTH

3. Second line options (only to be used if advised by endocrinology)

Glucocorticoids (inhibit 1,25OHD production)

- In lymphoma, other granulomatous disease or 25OHD poisoning
- Prednisolone 40mg daily, usually effective in 2 to 4 days

Calcitonin

- Can be considered if poor response to bisphosphonates

Calcimimetics (e.g. cinacalcet)

- Licensed for hypercalcaemia due to primary hyperparathyroidism, parathyroid carcinoma or renal failure

Parathyroidectomy

- Can be considered in acute presentation of primary hyperparathyroidism if severe hypercalcaemia and poor response to other measures

Refer to Endocrinology for further assessment. If

Management of incidental hypercalcaemia in a well patient

hypercalcaemia thought to be due to malignancy (known disease +/- suppressed PTH) may be more appropriate to refer to Oncology.

High calcium and high PTH [3]

Likely diagnosis is hyperparathyroidism. Patients will be considered for minimally invasive parathyroidectomy if:

- Fit and willing to consider surgery
- Have an adjusted serum calcium level that is 0.25mmol/L or more above the upper end of the reference range
- Symptomatic of hypercalcaemia or have evidence of end organ damage such as kidney stones or osteoporosis
- Age under 50 years
- Estimated glomerular filtration (eGFR) less than 60ml/min/1.73[2]
- Have other causes of raised PTH (such as vitamin D deficiency or FHH) excluded

Consider the following:[3]

- Correct 25(OH) vitamin D if deficient
- 24-hour urine collection for calcium to exclude FHH
- US renal tract and DEXA scan to look for end organ damage
- Referral to endocrine team, outpatient follow up likely to be appropriate

If surgery is not indicated, declined or contraindicated, consider the following:[3]

- Correction of vitamin D deficiency
- Medications to improve bone mineral density e.g. bisphosphonates
- Medications to control hypercalcaemia e.g. calcitonin or calcimimetics such as cinacalcet

High calcium and low PTH

Consider the following and treat underlying cause:[3]

- **Malignancy** (see Management of hypercalcaemia of malignancy MIL)
- **Granulomatous conditions** e.g. sarcoidosis, tuberculosis
- **Medications** e.g. thiazide diuretics, lithium, theophylline, vitamin A, vitamin D, calcium co-prescribed with antacids or vitamin D preparations (milk-alkali syndrome)
- **Chronic Kidney Disease** stage 4 or 5 or transplantation
- **Familial hypocalciuric hypercalcaemia**
- **Rhabdomyolysis**
- **Non-parathyroid endocrine disease** e.g. thyrotoxicosis, Addison's disease, phaeochromocytoma, vasoactive intestinal polypeptide hormone-producing tumour
- **Immobilisation** e.g. in Paget's disease

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References:

1. Society for Endocrinology (2013). Acute Hypercalcaemia Guideline. Accessed via: www.endocrinology.org/policy.
2. Lian, I.A., and Asberg, A. (2018). Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. *BMJ Open,* 8. https://doi.org/10.1136/bmjopen-2017-017703
3. Hypercalcaemia (2014). NICE Clinical Knowledge Summaries. https://cks.nice.org.uk/hypercalcaemia.
4. Summary of Product Characteristics. Zoledronic acid 4mg/5ml concentrate for solution for infusion. Last updated: 27th October 2017. Accessed via: https://www.medicines.org.uk/emc/product/5352/smpc
5. Summary of Product Characteristics. Disodium pamidronate 15mg/ml concentrate for solution for infusion. Last updated: 31st January 2019. Accessed via: https://www.medicines.org.uk/emc/product/2277/smpc

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