University Hospitals of Derby and Burton
NHS Foundation Trust

Hypocalcaemia - Full Clinical Guideline

Reference No: CG-PHARM/2018/004

Introduction

Hypocalcaemia is a potentially life threatening biochemical abnormality that carries serious risks if left untreated.

Aim and Purpose

The aim of the guideline is to ensure that calcium replacement therapy is safe and appropriate for the patient.

Scope

This guideline is applicable to all adult inpatients except those on ICU. This guideline is suitable for use in the vast majority of clinical situations but patients with chronic hypocalcaemia, recent head and neck surgery or CKD 4/5 should be discussed with the relevant speciality teams. For patients with end stage renal failure or those on dialysis refer to Renal. Tumour lysis must be considered in all haematology or oncology patients – seek senior advice.

Definition

Hypocalcaemia is a medical condition that can lead to life-threatening consequences if left untreated. Mild hypocalcaemia is often asymptomatic. The rate and magnitude of calcium depletion often determine the severity of symptoms.

Calcium Ranges

The normal reference range of albumin-corrected calcium in an adult is 2.2 – 2.6 mmol/L.

Mild hypocalcaemia – albumin-corrected calcium 2.0 - 2.20 mmol/L
Severe hypocalcaemia – albumin-corrected calcium ≤1.90 mmol/L

Severity also relates to presence of symptoms and ECG changes - severity in patients with albumin-corrected calcium 1.9 - 2.0 mmol/L is best judged by these factors.

Physiology of Calcium

Total calcium and corrected (adjusted for albumin) calcium results are reported. Caution must be taken when interpreting results. Please refer to adjusted or corrected calcium when making clinical decisions.

Approximately 40% of plasma calcium is bound to albumin. However, it is the unbound fraction that plays a large clinical role. The correction is not valid in acid-base disorders as calcium binding to albumin is affected by pH. For example, acidosis will increase the ionised plasma calcium, whereas alkalosis will have the opposite effect. Therefore a patient with acute respiratory alkalosis may exhibit signs of hypocalcaemia, such as paraesthesia.

Signs and symptoms of Hypocalcaemia

Extracellular calcium concentrations are important for the normal functioning of muscles and nerves. Thus, classic symptoms of hypocalcaemia are neuromuscular excitability in the form of muscle twitching, spasms, tingling, and numbness.

The main symptoms include:

Neuromuscular	Numbness Paraesthesia Muscle cramps Muscle weakness Laryngospasm/stridor Dysphagia Wheezing Tetany Tremors
Neurological	Changes in mental state - e.g. confusion, irritability, anxiety Seizures Fatigue Depression Personality changes
Cardiac	Prolonged QT interval, leading to heart block or VF Cardiac arrhythmias Coagulation irregularities Hypotension
Other symptoms	Chvostek and Trousseau signs Bronchospasm Nausea, vomiting, diarrhoea Coarse hair Brittle nails Dry skin Psoriasis

Causes

The cause of hypocalcaemia should be determined and if possible, measures should be taken to correct the underlying cause prior to calcium administration.

It should be recognised that a major cause in hospital inpatients is post-operative hypoparathyroidism following total parathyroidectomy (usually in the context of advanced Chronic Kidney Disease) or total thyroidectomy. If total thyroidectomy has recently occurred, commence treatment with alfacalcidol and calcium supplements with immediate effect including use of STAT doses of medications (delaying this action whilst awaiting further confirmatory biochemistry is likely to prolong hypocalcaemia and delay recovery.)

In more general terms, hypocalcaemia is normally caused by parathyroid hormone disturbances or low vitamin D levels.

This can be due to the following causes:

- Low dietary intake of vitamin D/reduced exposure to sunlight
- Reduced vitamin D synthesis (e.g. in renal failure, liver disease or anticonvulsant therapy)
- Hypomagnesaemia (needed for parathyroid hormone action) – Please refer to hypomagnesaemia guideline for further guidance
- Hyperphosphataemia
- Autoimmune hypoparathyroidism
- Pseudohypoparathyroidism (failure of target tissues to respond to hormone)
- Surgical removal of parathyroid glands/post-operative dysfunction after thyroidectomy
- Acute pancreatitis
- Septic shock
- Rhabdomyolysis
- Malignant disease
- Calcium malabsorption
- Massive blood transfusion
- Chronic renal insufficiency
- Drug-induced – e.g. some anticonvulsants, bisphosphonates, calcitonin, phosphate, colchicine overdose, foscarnet, radio contrast dye, ketoconazole and some antineoplastic agents.

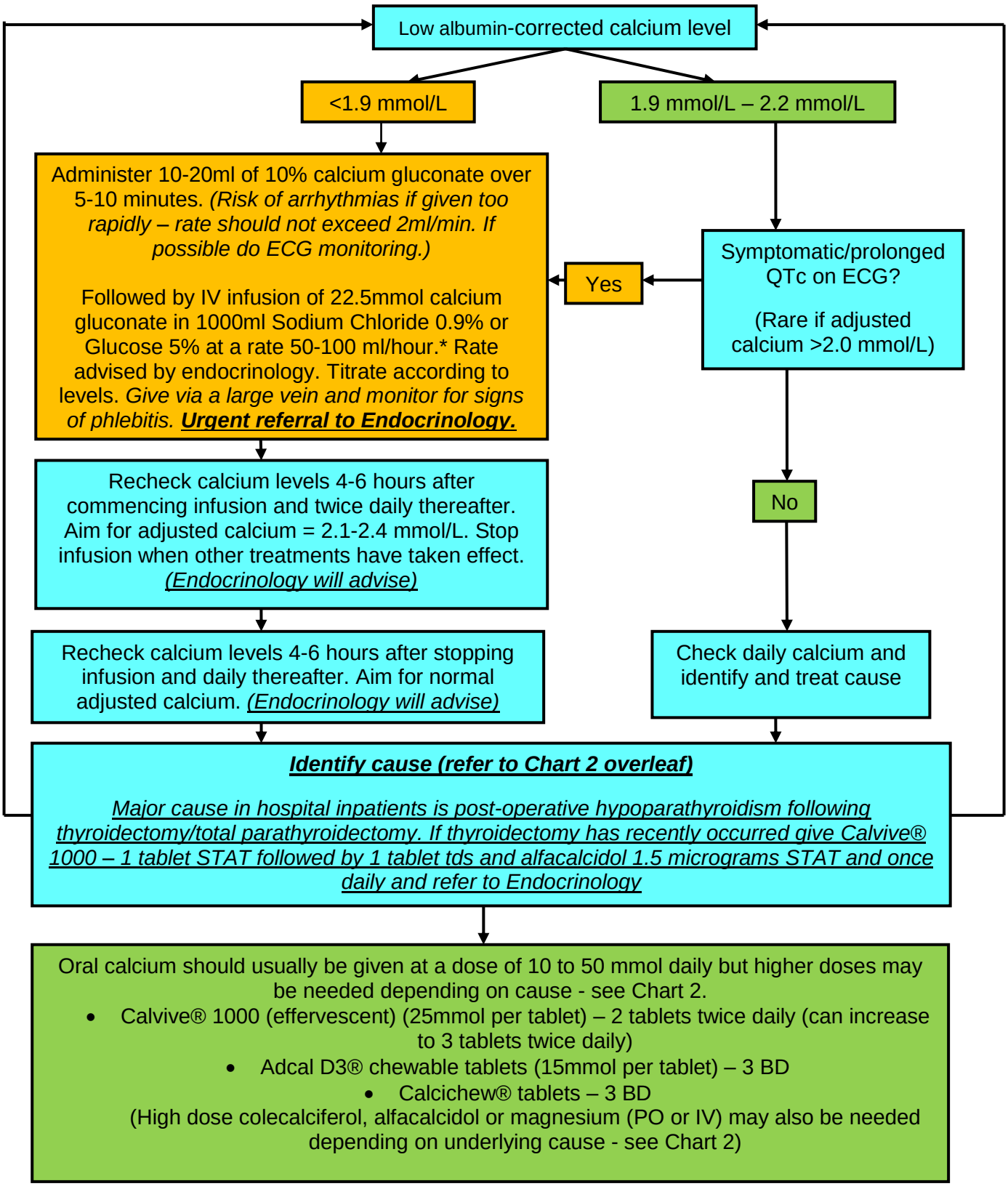
NB: A concurrent low phosphate level is more suggestive of vitamin D deficiency; a high phosphate level is more suggestive of hypoparathyroidism

Investigation and Treatment

The initial priority is to assess for severity of the problem and treat with IV calcium if indicated. Due to the potential for severe soft tissue damage from extravasation it is important not to treat patients unnecessarily with IV calcium. Please see Chart 1 below which outlines the steps required to assess severity and tailor immediate action to that assessment.

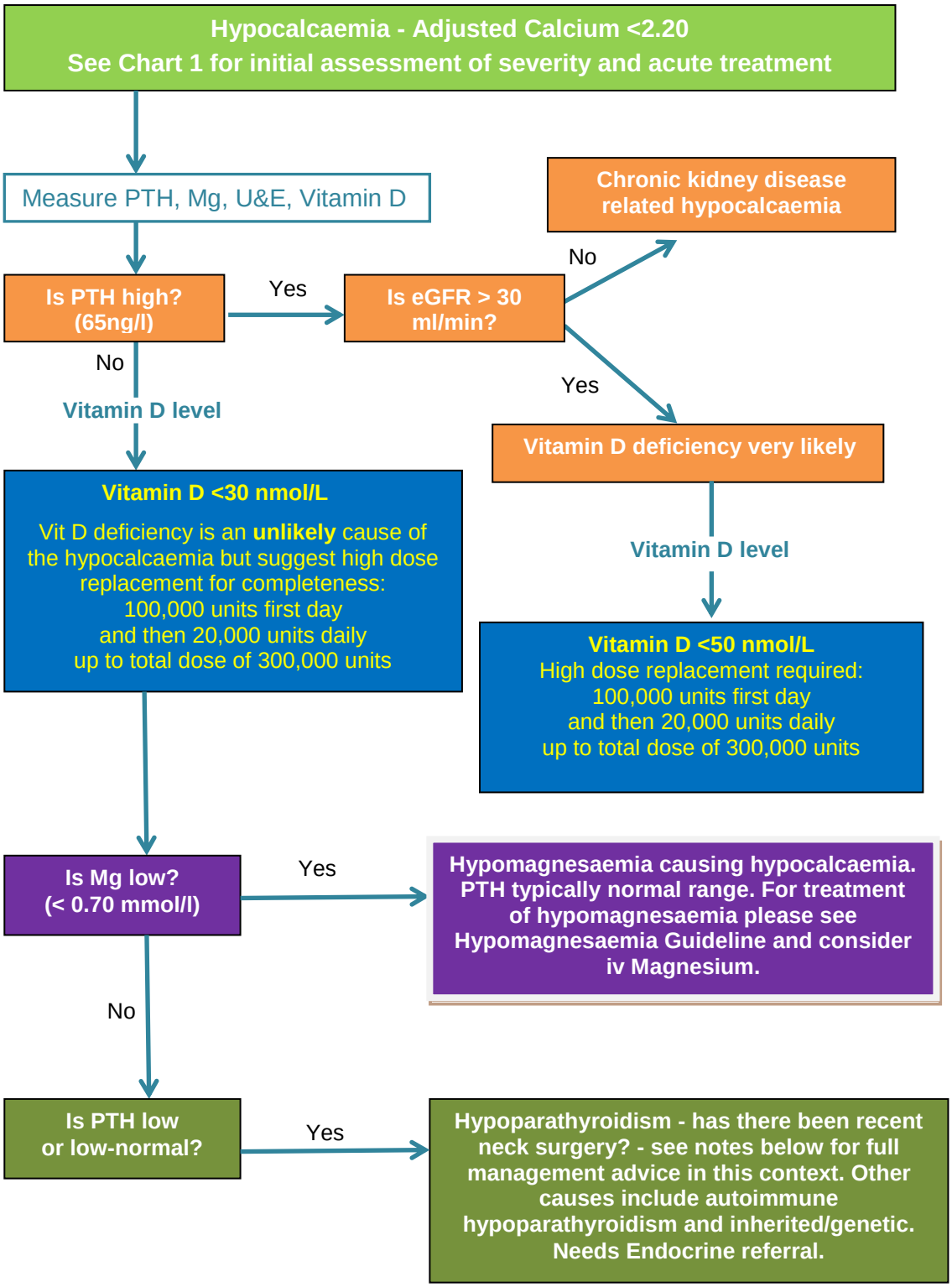
It is ***essential*** that the underlying cause of hypocalcaemia is identified and addressed regardless of extent of hypocalcaemia. Failure to do this in patients with mild hypocalcaemia will risk severe hypocalcaemia. Failure to do this in patients treated with IV calcium will lead to an extended (potentially hazardous) IV treatment and/or recurrence upon cessation of IV calcium. Tests to identify causes always include corrected calcium, PTH, Vitamin D, U&E's and Magnesium levels. The initial interpretation of these tests is described in Chart 2, but in inpatients with recent complex/severe illness, advice from relevant speciality teams will be needed if the cause is not derived from Chart 2.

Chart 1- Management of Hypocalcaemia in Inpatients



*Please note – 22.5mmol calcium gluconate infusions require aseptic manufacture by pharmacy (at RDH only). Whilst this is being prepared, a second bolus may be given if deemed appropriate.

Chart 2 - Initial investigations for cause of hypocalcaemia



Further information on Specific Cause

Post total (or 'completion') thyroidectomy This generally occurs due to hypoparathyroidism as a consequence of the surgery. This can be temporary or permanent. The fall in calcium is rapid so is more likely to be symptomatic and require treatment. If total thyroidectomy has recently occurred, commence treatment with alfacalcidol and calcium supplements with immediate effect including use of STAT doses of medications (delaying this action whilst awaiting further confirmatory biochemistry is likely to prolong hypocalcaemia and delay recovery.) See Chart 1 for further details of management. Involve Endocrinology at the earliest opportunity. For full details on prevention and management of hypocalcaemia following total/completion thyroidectomy see section at end of this guideline*.

Post total parathyroidectomy This can be in the context of advanced Chronic Kidney disease - involve Nephrology team. Endocrinology patients also occasionally have a total parathyroidectomy (as opposed to the more frequent partial parathyroidectomy)- these patients should be proactively managed with alfacalcidol and calcium supplements +/- IV calcium gluconate as per the thyroidectomy group described above and referred to Endocrinology. Hypocalcaemia after partial parathyroidectomy is much rarer; if it does occur it could indicate Hungry Bone Syndrome - refer to Endocrinology and manage as per the 'thyroidectomy' group whilst awaiting further advice.

Chronic Kidney Disease Hypocalcaemia is due to the reduction in the renal activation of vitamin D, which normally increases circulating calcium by increasing intestinal absorption.

Hypomagnesaemia Hypomagnesaemia is a common cause of hypocalcaemia, both by inducing resistance to parathyroid hormone (PTH) and by diminishing its secretion. If patient is asymptomatic, correct the hypomagnesaemia first before giving calcium, as this may lead to a spontaneous normalisation of calcium concentrations (see hypomagnesaemia guidelines).

Hypoparathyroidism Parathyroid hormone increases vitamin D activity via hydroxylation, increases bone resorption and decreases renal calcium excretion. Most patients with hypoparathyroidism require lifelong calcium and vitamin D supplementation. An exception is the occurrence of transient hypoparathyroidism after thyroidectomy or parathyroidectomy as detailed above.

Shared care guidelines The following guidelines are available for primary and secondary care. They refer to the management of hypocalcaemia detected in Primary Care and the management of associated conditions.

Shared care guidelines are available from:
http://www.derbyhospitals.nhs.uk/primary/pathology/shared-care-pathology-guidelines/

Notes

Calcium Gluconate – 10ml of 10% calcium gluconate contains 2.25mmol of calcium. Some centres use 20ml as a bolus over 10 minutes without apparent problem. This is the preferred calcium preparation for any patient with peripheral access. Intravenous calcium in presence of high phosphate can precipitate calciphylaxis and renal advice should be taken.

Calcium chloride – is an option if using central access - it may offer more stable IV levels during infusion compared with calcium gluconate but concerns about severe tissue injury with peripheral use mean it is not appropriate for peripheral vein use. For ICU use only.

Adcal D3 – Annotate chart with *'short term for hypocalcaemia – review ongoing need'* in the additional information box on EPMA prescription.

Interactions – Oral calcium supplements reduce the absorption of a number of other drugs, and should not be taken at the same time of day. These include tetracyclines, ciprofloxacin and bisphosphonates.

Oral calcium carbonate preparations (eg. Adcal D3) can cause GI symptoms and are unreliably absorbed if taken alongside PPIs. Please contact pharmacy for advice on management.

Cautions and contraindications – Calcium administration is contraindicated in those with ventricular fibrillation and patients with hypercalcaemia.

Patients on digoxin – These patients should be monitored closely as calcium may precipitate digitalis toxicity.

Adverse effects of calcium therapy – Hypercalcaemia – refer to Chart 1 and monitor levels. GI side effects including constipation. Rapid IV administration may result in venous irritation, hot flushes and peripheral vasodilation. Rapid administration may also result in hypotension, bradycardia, arrhythmias, syncope and cardiac arrest.

***Full details re Prevention and Management of Post-Operative Hypocalcaemia following Total Thyroidectomy**

Introduction

Post-operative hypocalcaemia following Total Thyroidectomy is a common event.
Contemporary British data suggests nearly 30% incidence of temporary hypocalcaemia (BAETS Audit data)
Permanent hypoparathyroidism is far less common- typically 1-2%
Certain groups of patient may be more at risk;

- Thyroid cancer patients- especially in the context of level VI neck dissection
- Young females with Graves disease

1. Pre-operative loading of vitamin D

Pre-operative vitamin-D deficiency has been shown to increase the chance of post-thyroidectomy hypocalcaemia.

Check serum calcium, phosphate and vitamin D
If calcium not raised and 25OH-vitamin D <50 nmol/l give Colecalciferol 20000 units/day for 14 days and then maintenance dose of 800 units/day (eg Fultium D3)
If surgery is planned within 2 weeks it is acceptable to prescribe 800 units/day colecalciferol pre-op without calcium/vit D check

2. Early identification and treatment of patients at risk of post-operative hypoparathyroidism

All patients to commence 1g elemental calcium (eg Calvive 1000) twice per day immediately post-op.

Low serum PTH level checked early post-thyroidectomy has been shown to predict the chance hypocalcaemia and has also been used to prioritise patients for early commencement of 1α-hydroxylated vitamin D analogues, reduce hypocalcaemia related complications and facilitate early discharge from hospital.

-Early postoperative low PTH result prompts treatment to prevent hypocalcaemia and reduce length of stay.
-Normal PTH prompts consideration for early discharge from hospital.

See Chart 3 for suggested use of early PTH and interpretation of results.

3. Treatment of Post-operative hypoparathyroidism

The mainstay of treatment is adequate calcium supplementation and this is recommended immediately post op in all patients.

Chart 3 outlines the suggested intensification of treatment to include higher dose calcium supplementation and addition of hydroxylated vitamin D (such as alfacalcidol) in patients depending on early post-op PTH and subsequent calcium monitoring.

Use of colecalciferol (Vitamin D3) post-operatively is not rational because the patients who develop hypoparathyroidism will not be able to hydroxylate Vitamin D3 to produce the active form- hence alfacalcidol is recommended when vitamin D is required.

4. Subsequent progress

Patients sent home on calcium supplements alone
Calcium should continue on discharge until review in the endocrine clinic in 4- 6 weeks. Please provide patients with request forms for calcium check before their follow up appointment and inform Endocrinology Specialist Nurse or Registrar/Consultant to follow up in clinic*

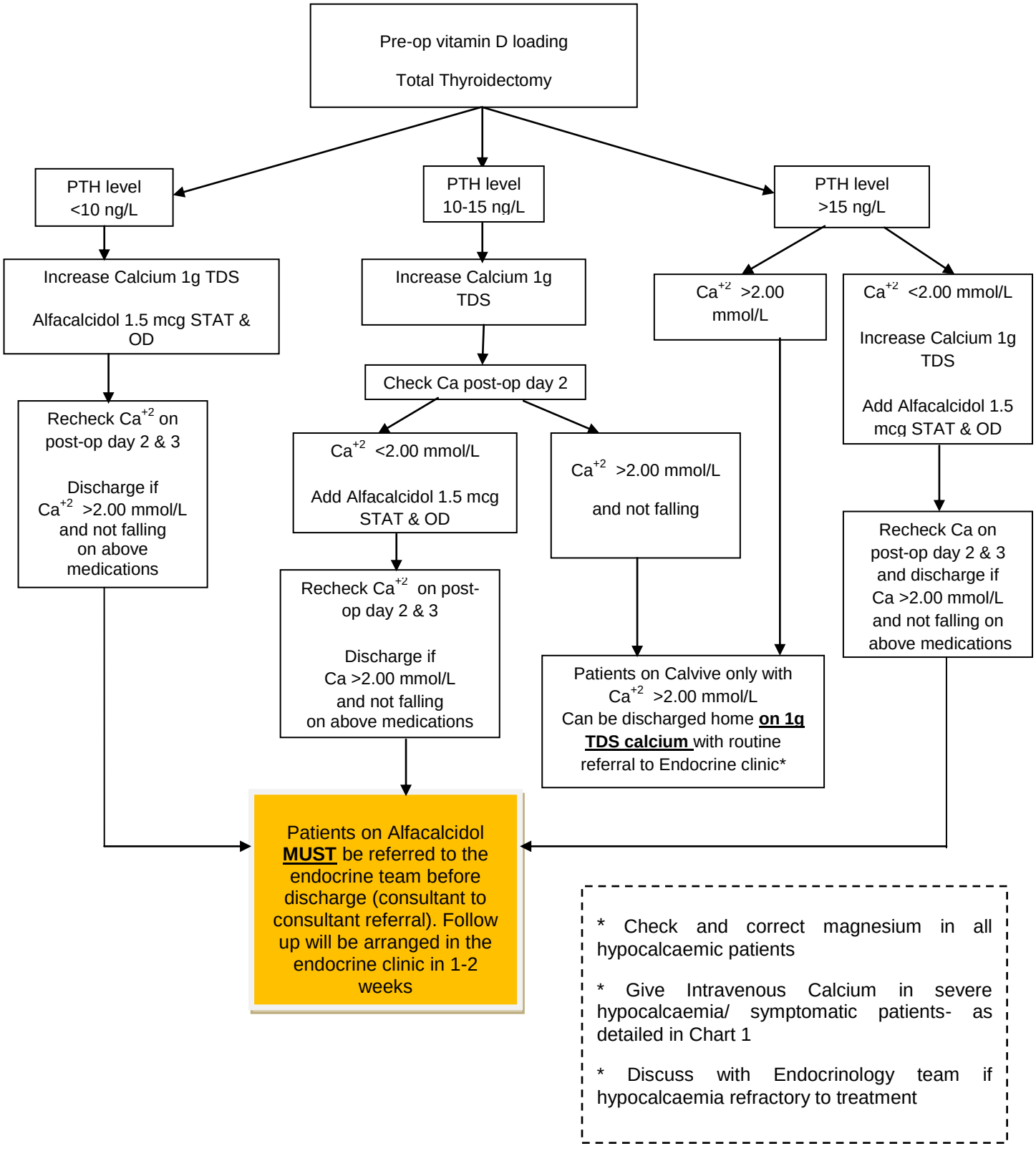
Patients sent home on calcium supplements *and* alfacalcidol
These patients will require ongoing Endocrinology involvement. The majority will be able to stop calcium and alfacalcidol in due course. Please refer to the endocrine team before the patient is discharged from hospital (this is via Consultant 2 Consultant referral on ExtraMed e-Whiteboard).

Please provide three request forms for calcium, phosphate and PTH to the patient at the time of discharge. Initial plans are for the first blood test to take place 2-3 days post discharge with subsequent tests at weekly intervals according to progress.

* **Endocrine Nurse Specialist/Consultant should be notified by the waiting list office or secretary in advance for all elective total/completion thyroidectomies so that appropriate follow up arrangements can be preplanned- these arrangements will still need to be confirmed at the time of discharge from hospital.**

The long term aim of Endocrine follow-up is to identify patients who have only temporary hypoparathyroidism- and to stop calcium and vitamin D supplements where appropriate and avoid severe hypercalcaemia due to inappropriately continued treatment.

Chart 3 Prevention and Treatment of Post Thyroidectomy Hypoparathyroidism



5. Audit Criteria- total and completion thyroidectomy patients

Routine collection of the following data is suggested;

Incidence of early hypocalcaemia post-thyroidectomy-
Defined as lowest inpatient Adjusted Calcium <2.10
(Surgical Audit)

Incidence of permanent hypoparathyrodism
Defined as ongoing requirement for alfacalcidol or calcitriol 12 months post-op
(Endocrine Audit but denominator derived from Surgical data)

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Documentation Controls

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