MANAGEMENT of MALIGNANT HYPERCALCAEMIA

TARGET AUDIENCE	Primary and Secondary Care Practitioners
PATIENT GROUP	Adult patients with palliative care needs

Clinical Guidelines Summary

- Hypercalcaemia is defined as elevated adjusted calcium levels as per locally agreed limits. In NHS Lanarkshire this relates to adjusted calcium >2.6mmol/l
- People with symptoms or with moderate /severe hypercalcaemia (>3.0mmol/L) will usually be admitted to hospital for management
- Pre-hydration should be undertaken prior to definitive bisphosphonate therapy

- The NHS Lanarkshire bisphosphonate therapy of choice is zoledronic acid
- Zoledronic acid is delivered as an infusion of 4mg of zoledronic acid in 100ml NaCl 0.9% over at least 15 minutes
- Zoledronic acid requires dose adjustment in the event of renal impairment

- Calcium levels should be rechecked after 5 days
- If calcium has returned to normal and patients are no longer symptomatic, calcium levels should be monitored every 3-4 weeks or if symptoms of hypercalcaemia occur

- **It may not be appropriate to treat all people with malignant hypercalcaemia**

Management of Malignant Hypercalcaemia

This guideline has been produced in line with the national Scottish Palliative Care Guideline: Hypercalcaemia[1] and the NICE guidelines: Hypercalcaemia – known malignancy[2].

Background

Hypercalcaemia is defined as elevated adjusted calcium levels as per locally agreed limits. In NHS Lanarkshire this relates to adjusted calcium >2.6mmol/l.

Hypercalcaemia is the most common metabolic disorder in people with cancer and although it may be seen with any tumour type it is most common in lung cancer, breast cancer and multiple myeloma[3]. Hypercalcaemia occurs due to several different factors in malignancy:

- Release of parathyroid hormone-related peptide
- Osteolytic metastases resulting in the release of mineralised calcium
- Ectopic activity of 1-alpha-hydroxylase
- Ectopic production of parathyroid related hormone[4]

Presentation

Symptoms of hypercalcaemia are varied and can often be subtle. They are more commonly seen in cases of moderate / severe hypercalcaemia (defined as >3.0mmol/l) however, it is important to be vigilant as symptoms can occur at any level.

Common symptoms include malaise, thirst, anorexia, nausea, constipation and polyuria. Severe symptoms include vomiting, ileus, delirium, seizures, drowsiness and coma[1,5]. Hypercalcaemia has also been known to reduce the pain threshold and is recognised as a predictor for poor prognosis[6].

Management

Who to treat

The aim of treatment should be to improve symptoms and reduce corrected calcium to within the normal range.

It may not be appropriate to treat all people with malignant hypercalcaemia. In those who are in the last days of life, it may be decided by an experienced clinician that invasive investigations and treatments may not be beneficial.

People with symptoms or with moderate /severe hypercalcaemia (>3.0mmol/L) will usually be admitted to hospital for management as detailed below.

Asymptomatic people with mild hypercalcaemia (3.0mmol/L or less) should be assessed on a case by case basis. Advice may be sought from specialists and patients should be involved in discussions regarding the appropriateness of treatment. In some circumstances it may be appropriate to advise increased oral intake of fluid, avoid exacerbating drugs or diet and vigilance regarding symptoms[1,2].

Patients with myeloma or suspected myeloma should be discussed with haematology.

Discontinuation of other drugs

A full medicines reconciliation should be undertaken to identify any drugs that may be exacerbating hypercalcaemia. These commonly include calcium-containing vitamin supplements and drugs which affect renal blood flow such as non-steroidal anti-inflammatories and thiazide diuretics[7].

Pre-hydration

Pre-hydration should be undertaken prior to definitive bisphosphonate therapy. This has a number of benefits including: replacing lost sodium, increasing glomerular filtration rate and circulating volume and promoting urinary calcium excretion.

Sodium chloride 0.9% is the IV fluid of choice and ideally patients should receive 1-3 litres over 24hours prior to calcium levels and renal function being rechecked the following day. Tailor fluid regime to the individual and monitor for fluid overload if renal impairment, the elderly or patients with congestive heart failure. In patients with symptomatic hypercalcaemia, hydration is unlikely to be a definitive treatment, even if there is an improvement in calcium levels it will likely increase again when fluids are discontinued. Bisphosphonates will most likely be required for longer term control of calcium levels.

Bisphosphonate Therapy

The NHS Lanarkshire bisphosphonate therapy of choice is zoledronic acid. Other options of pamidronate (an alternative bisphosphonate) and denosumab (a human monoclonal antibody) can be considered in special circumstances under the advice of palliative care, oncology or haematology.

Zoledronic acid is delivered as an infusion of 4mg of zoledronic acid in 100ml NaCl 0.9% over at least 15 minutes. Zoledronic acid has been shown to be superior to pamidronate with regards to: longer duration of effect, shorter infusion duration, simpler dosing and similar safety data[1,7].

Common side effects may include hypocalcaemia, influenza like illness, nausea and vomiting and renal impairment. Potential adverse events such as atypical femoral fractures, osteonecrosis of the jaw and osteonecrosis of the external auditory canal are uncommon and are mainly associated with long-term therapy.

Dose Adjustments in Renal Impairment

Zoledronic acid requires dose adjustment in the event of renal impairment. Refer to SPC for further information. Zoledronic acid should be avoided if serum creatinine is >400 micromol/litre or creatinine clearance <30ml/min[8,9,]. Advice from palliative care, oncology or haematology should be sought in these circumstances.

Follow Up

Following bisphosphonate administration, IV fluids should be continued until patients are deemed to have adequate hydration by an experienced clinician. Renal function should be monitored.

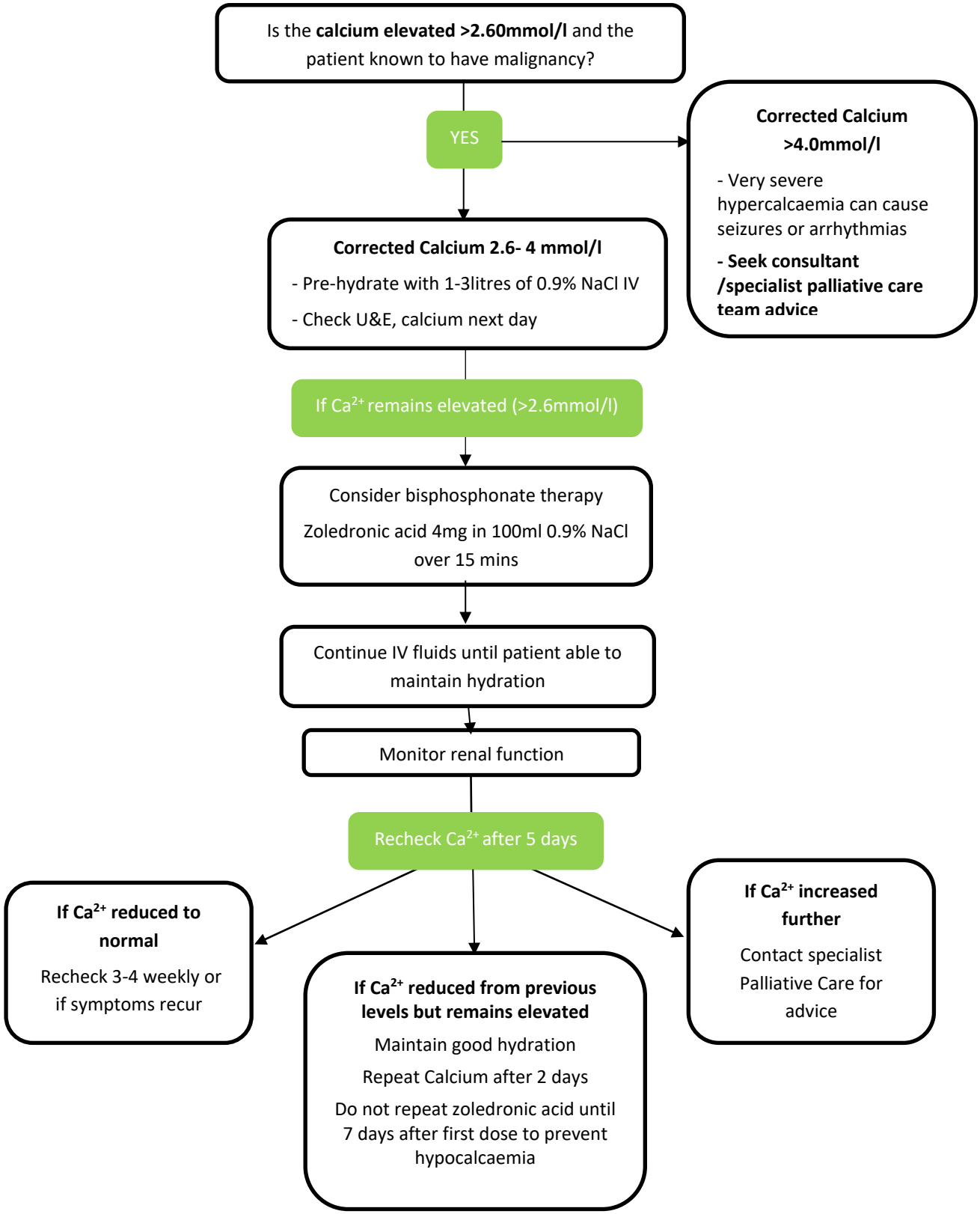
Calcium levels should be rechecked after 5 days. It is rarely helpful to check the calcium levels before this, and in fact can cause unnecessary concern, as calcium levels will take a few days to fall. In the event of increased post-treatment calcium levels, specialist advice should be sought on next steps.

If calcium has returned to normal and patients are no longer symptomatic, calcium levels should be monitored every 3-4 weeks or if symptoms of hypercalcaemia occur[1,5,].

Monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated

Management of Malignant Hypercalcaemia

Advice can always be sought via the on-call Specialist Palliative Care Team



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References/Evidence

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Appendices

1. Governance information for Guidance document

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