NHS
Kent and Medway
Cancer Collaborative

Hypercalcaemia Guidelines

Network Guidance Document

Kent & Medway Cancer Collaborative

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1.0 SIGNS AND SYMPTOMS OF HYPERCALCAEMIA OF MALIGNANCY

Hypercalcaemia is defined as a serum calcium concentration of 2.65mmol/L(or higher) on two occasions, following adjustment for the serum albumin concentration. It might be classified according to severity:

- Mild-adjusted serum calcium concentration of 2.65-3.00 mmols/L
- Moderate- adjusted serum calcium concentration of 3.01-3.40mmols/L
- Severe-adjusted serum calcium concentration of greater than 3.40mmol/L
- Calcium over 3.5mmol/l gives a significant risk of cardiac arrest and therefore must be treated more aggressively. Some patients are more at risk e.g.
    - Patients with hypokalaemia
    - Patients on digoxin, even more so if toxic
    - Patients with pre-existing heart disease

In malignancy, hypercalcaemia most commonly results from direct bony invasion by tumour cells rather than humorally mediated hypercalcaemia.

1.1 Symptoms

- Skeletal — bone pain, fractures (osteoporotic in hyperparathyroidism or pathological in malignancy).
- Neuromuscular and neuropsychiatric — drowsiness, delirium, coma, fatigue, muscle weakness, impaired concentration and memory, depression, and neurological signs (for example upper motor neurone deficits and ataxia).
- Gastrointestinal — nausea, vomiting, anorexia, weight loss, constipation, abdominal pain, peptic ulcer, and pancreatitis.
- Renal — polyuria, polydipsia, and dehydration; renal colic and renal impairment.
- Cardiovascular — hypertension, and shortened QT interval on electrocardiogram (ECG).
- Other — itching, keratitis, conjunctivitis, and corneal calcification.

1.2 Patients at Risk

Tumour types associated with hypercalcaemia

- Lung 35%
- Breast 25%
- Haematological 14%
- Squamous (head & neck) 6%
- Genito-urinary 6%
- Other 15%

2.0 MANAGEMENT OF MALIGNANT HYPERCALCAEMIA

- Calcium adjusted for albumin
  serum Ca mmol/L + [(40-albumin) x 0.02]

- Assess hydration state clinically and according to U&E.
- Commence IV fluids, 4-6 litres sodium chloride 0.9% per 24 hours if dehydrated.
- Caution, monitor for fluid overload if renal impairment, the elderly or patients with congestive heart failure.
- Re-assess corrected calcium level. Calcium levels should be monitored daily. If < 3.0 after hydration, it is likely that the patient will still require IV bisphosphonate. If patient is adequately hydrated and has a normal urea then initiate bisphosphonate as soon as possible.

- Review concomitant medication that may contribute to increased calcium such as calcium supplements, thiazide diuretics and vitamin D.
- Pamidronate:

Corrected Calcium	Pamidronate dose	Administration
Up to 3.0 mmol/l	15-30mg	250ml Sodium Chloride 0.9% over 30 minutes
3.0 – 3.5 mmol/l	30-60mg	250ml Sodium Chloride 0.9% over 1 hour
3.5 – 4.0 mmol/l	60-90mg	500ml Sodium Chloride 0.9% over 90 minutes
>4.0 mmol/l	90mg	500ml Sodium Chloride 0.9% over 90 minutes

A significant decrease in serum calcium is generally observed 24-48 hours after administration of Disodium Pamidronate Injection, and normalisation is usually achieved within 3-7 days. Dose can be repeated at 3 - 4 week intervals.

The total dose of pamidronate may be administered either as a single infusion or in multiple infusions over 2 – 4 consecutive days.

The maximum dose per treatment course is 90mg for both initial and repeated courses.

Dosage in renal failure (SPC): Pamidronate should not be administered to patients with severe renal impairment (creatinine clearance < 30 mL/min) unless in cases of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk. It is recommended that for patients with established or suspected renal impairment, the infusion rate should not exceed 20mg/hour.

- Zoledronic acid (Zometa®) can be used routinely for tumour-induced hypercalcaemia. The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid, dose adjustment is not necessary in hypercalcemia of malignancy when serum creatinine < 400 µmol/l. If serum creatinine >400 µmol/l consider alternative treatment e.g. denosumab.
- Re-treatment with zolendronic acid may be considered after a minimum of 7 days, consideration should be given to the increased risk of osteonecrosis of the jaw before proceeding.

3.0 POTENTIAL SIDE EFFECTS OF BISPHOSPHONATES: (FOR FULL LIST, SEE MANUFACTURERS' SPCS)

Pamidronate is less likely than zolendronic acid to cause hypocalcaemia and osteonecrosis of the jaw.

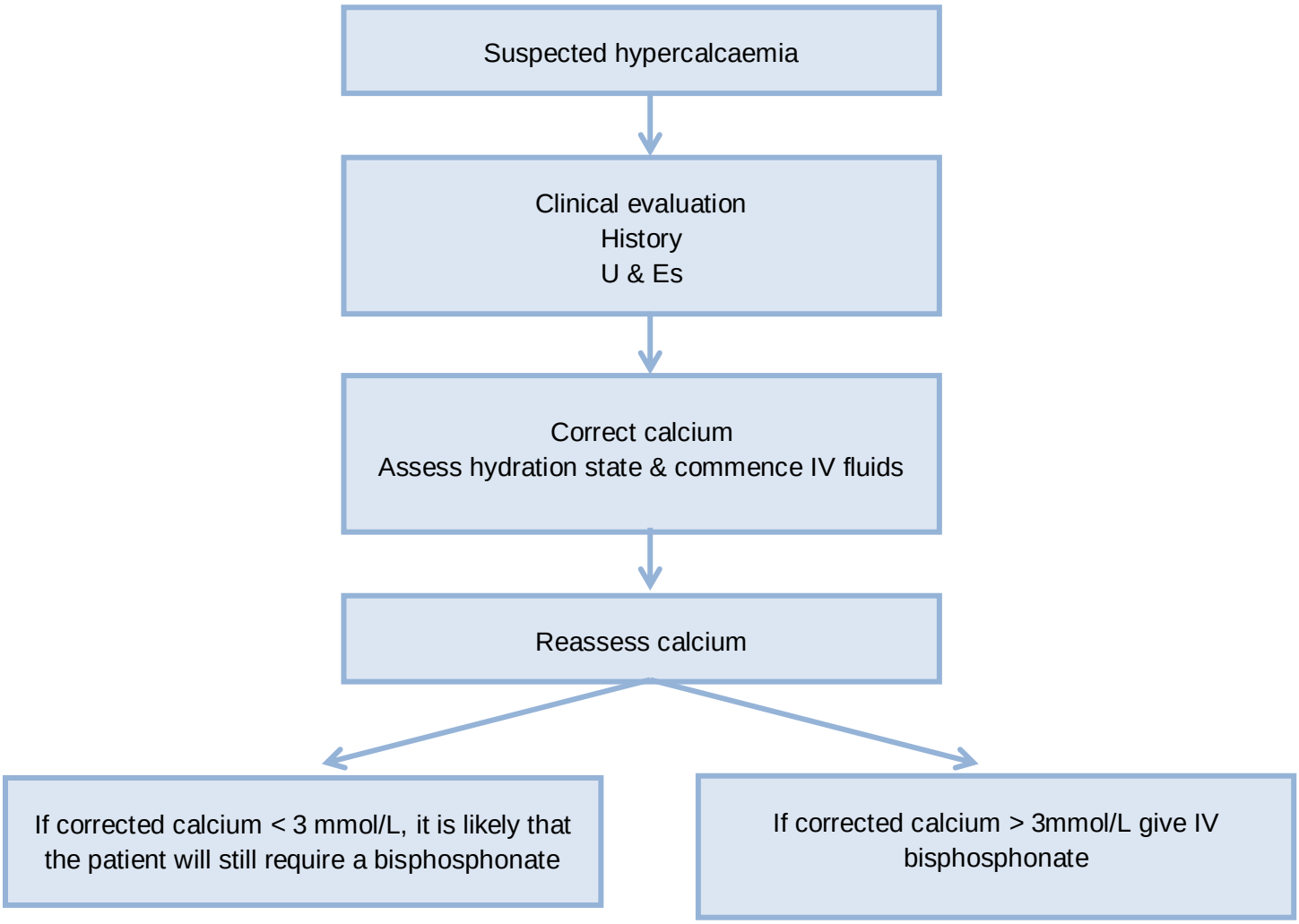
- **Very common (>10%):** transient pyrexia and influenza-like symptoms (more common with IV nitrogen-containing bisphosphonates), fatigue, headache, anxiety, hypertension, anaemia, thrombocytopenia, cough, arthralgia, myalgia, bone pain, asymptomatic hypocalcaemia, hypomagnesaemia, hypophosphataemia. Oral preparations in particular may cause anorexia, dyspepsia, nausea, vomiting, abdominal pain, diarrhoea or constipation.
- **Common (<10%, >1%):** sleep disturbance, psychosis, tachycardia, atrial fibrillation or flutter, syncope, dyspnoea, leucopenia, infusion site reactions, deterioration in renal function, increased serum creatinine, hypokalaemia.
- **Rare (<0.1%, >0.01%):** ocular inflammation, angioedema, collapsing focal segmental glomerulosclerosis (disodium pamidronate), nephrotic syndrome (disodium pamidronate), symptomatic hypocalcaemia (e.g. tetany).
- **Very rare (<0.01%):** anaphylaxis, bronchospasm, osteonecrosis of the jaw.

4.0 OTHER TREATMENT OPTIONS

- Consider the use of calcitonin to reduce serum calcium levels to safe levels whilst bisphosphonates take effect. However calcitonin is highly emetogenic and loses its effect with prolonged use.
- For patients with treatment resistant hypercalceamia previously treated with zolendronic acid, consider the use of pamidronate. Denosumab, where funding is available, may be considered if the patient has treatment resistant hypercalceamia or in patients with renal failure when bisphosphonates cannot be used.

Malignant hypercalceamia is likely to recur continue to monitor patients after discharge.

5.0 DIAGNOSTIC ALGORITHM FOR HYPERCALCAEMIA OF MALIGNANCY



6.0 REFERENCES

- NICE August 2019 revised: Hypercalcaemia CKS. Available from http://cks.nice.org.uk/hypercalcaemia.
- Society of Endocrinology 2013. Emergency Endocrine Guidance. Acute Hypercalcaemia. Available from http://www.rcem.ac.uk/docs
- Wockhardt UK LTD SPC 2nd April 2008. Disodium Pamidronate concentration for infusion. Last reviewed 18/01/2018. Available from http://www.medicines.org.uk

7.0 GLOSSARY

Acronyms in common usage throughout KMCC documentation

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website

TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

8.0 DOCUMENT ADMINISTRATION

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Co-author(s)	Caroline Waters
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