

HYPERCALCEMIA IN MALIGNANT DISEASE (PALLIATIVE MANAGEMENT)

Rationale

This guideline is adapted for inter-professional primary care providers working in various settings in VIHA and any other clinical practice setting in which a user may see the guidelines as applicable.

Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of hypercalcemia. This guideline does not address disease specific approaches in the management of hypercalcemia.

Hypercalcemia is the most frequent metabolic emergency in oncology and occurs in 10% to 40% of cancer patients.⁽¹⁻³⁾ Hypercalcemia most commonly occurs in patients with advanced cancer and is an indicator of poor prognosis.^(1, 2, 4-6)

Definition of Terms

Hypercalcemia is defined as serum calcium (corrected) greater than 2.6 mmol/L.⁽³⁾

Standard of Care

1. Assessment
2. Diagnosis
3. Education
4. Treatment: Non-pharmacological
5. Treatment: Pharmacological

Recommendation 1

Hypercalcemia Assessment

Ongoing comprehensive assessment is the foundation of effective management of hypercalcemia, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.

*Table 1: Hypercalcemia Assessment using Acronym O, P, Q, R, S, T, U and V**

O Onset	When did it begin? How often does it occur?
P Provoking / Palliating	What brings it on? What makes it better? What makes it worse?
Q Quality	What does it feel like? Can you describe it?
R Region / Radiation	
S Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right Now? At Best? At Worst? On Average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom? Nausea/vomiting, constipation, weakness, loss of appetite, confusion or agitation?
T Treatment	What medications and treatments are you currently using? How effective are these? Do you have any side effects from the medications and treatments? What medications and treatments have you used in the past?
U Understanding/ Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and / or your family?
V Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?

*** also include a Physical Assessment (as appropriate for symptom)**

Signs And Symptoms:

The severity of symptoms are not always related to the degree of hypercalcemia but often reflect the rapidity of onset.⁽⁴⁾ Patients do not always exhibit all of the clinical features. The onset of hypercalcemia may be insidious.⁽³⁾

- **Neurological:** fatigue, lethargy, confusion, myopathy, hyporeflexia, seizures, psychosis and coma.⁽⁷⁾ The most frequent effect of hypercalcemia is delirium.⁽⁸⁾
- **General:** dehydration, polydipsia, polyuria, pruritis.^(7, 9) Weakness and bone pain may also be present.⁽⁸⁾
- **GI:** anorexia, nausea and vomiting, weight loss, constipation, ileus and abdominal pain.⁽⁷⁻⁹⁾
- **Cardiac:** shortened Q-T interval, prolonged P-R interval, wide T waves, ventricular and atrial arrhythmias and bradycardia.^(7, 9) Arrhythmias, such as bradycardia, can be fatal.⁽⁸⁾
- **Renal:** polyuria, polydipsia, dehydration and development of kidney stones.⁽⁸⁾
- **Early:** polyuria, nocturia, polydipsia, dehydration, anorexia, easy fatigability, weakness, hyporeflexia, pain may be precipitated or exacerbated by hypercalcemia.⁽⁴⁾
- **Late:** apathy, irritability, depression, decreased ability to concentrate, obtundation, coma, profound muscle weakness, nausea and vomiting, constipation, increased gastric acid secretion, acute pancreatitis, pruritus, visual disturbances, sudden death from cardiac dysrhythmias may occur if calcium rises fast, especially in patients taking digoxin.⁽⁴⁾

Laboratory Studies:

Always relate serum calcium levels to serum albumin levels

Method for Calculating Correction of Calcium Level to Reflect Albumin Level:

- If serum albumin is less than 40 grams per litre, increase measured calcium by 0.20 mmol per litre for every 10 grams of albumin below 40 grams per litre.
- If serum albumin is greater than 40 grams per litre, reduce measured calcium by 0.20 mmol per litre for every 10 grams of albumin over 40 grams per litre.

Alternatively:

- Corrected calcium (mmol/L) = Measured calcium (mmol/L) + [0.02 x (40 – measured albumin g/L)].^(1, 3, 8)

Other possible abnormal results:

- Alkaline phosphatase – usually elevated, except in myeloma.⁽⁴⁾

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- Chloride may be elevated in primary hyperparathyroidism.(4, 5)
- BUN, creatinine may be elevated from renal damage.(4)
- Electrocardiogram – prolonged PR interval, widened QRS complex, shortened QT, widened T wave, bradycardia.(4)

Recommendation 2

Diagnosis

Management should include treating reversible causes where possible and desirable according to the goals of care. The most significant intervention in the management of hypercalcemia is identifying underlying cause(s) and treating as appropriate. While underlying cause(s) may be evident, treatment may not be indicated, depending on the stage of disease.

Whether or not the underlying cause(s) can be relieved or treated, all patients will benefit from management of the symptom using education, hydration and medications.

Identifying the underlying etiology of hypercalcemia is essential in determining the interventions required.

Causes:

- The majority of cases of humoral hypercalcemia of malignancy are associated with impaired gut absorption of calcium and low levels of vitamin D.(9)
- Secretion of parathyroid hormone-related protein by the tumour.(6, 8, 10) This occurs in 80% of hypercalcemia cases.(8)
- Osteolytic skeletal metastases.(4, 8) The extent of metastases does not correlate well with level of calcium.(4)
- Decreased renal clearance of calcium.(9)
- Increased gastrointestinal absorption of calcium in response to elevated levels of 1,25-dihydroxycholecalciferol (1,25 (OH)2D3, calcitriol) resulting from ectopic production of this vitamin by haematological neoplasms – this occurs rarely.(9)

Tumours most often associated with hypercalcemia:

- Multiple myeloma – 40% to 50%.(4, 5)
- Breast – greater than 20% of cases with cancer-related hypercalcemia.(4, 5)
- Lung – 20%, usually squamous cell, sometimes adenocarcinoma, rarely small cell.(4)
- Hypernephroma.(4)
- Squamous cell cancers of the head and neck and esophagus.(4)
- Thyroid.(4)
- Rarely or never – prostate or colorectal cancer.(4)

Recommendation 3

Education

Teach patients at risk and their caregivers the signs and symptoms of hypercalcemia to promote early recognition of acute rises in serum calcium.⁽⁴⁾

Recommendation 4

Treatment: Non-pharmacological

Re-hydration:

- Hydration alone may be sufficient for asymptomatic patients with borderline serum calcium.⁽⁴⁾
- Adequate hydration reduces serum calcium by a median of 0.25 mmol per litre.⁽³⁾
- All hypercalcemic patients are dehydrated due to polyuria and vomiting.⁽⁴⁾
- Hydration is appropriate for treatable hypercalcemia.⁽¹¹⁾ Re-hydration with 2 to 3 litres per day is now the accepted practice with daily serum electrolyte measurement to prevent hypokalemia and hyponatremia for cases of severe or symptomatic hypercalcemia.^(4, 9)
- Increase patient's oral fluid intake to 2 to 3 litres per day, as tolerated.⁽⁴⁾
- Most patients are usually 4 litres behind in their overall fluid balance when a diagnosis of hypercalcemia is made. Rehydration with normal saline should commence at 100 to 120 mL per hour I.V. or by hypodermoclysis based on patient's cardiac status (e.g., a slower rate should be used in patients prone to CHF).

Mobilization:

- Mobilization of the patient is important, in that it slows down the loss of skeletal calcium associated with immobility.⁽⁴⁾

Diet:

- Low calcium diet is needed to control hypercalcemia caused by elevated 1,25 (OH)2D3 but they are unpalatable, impractical and exacerbate malnutrition and have no place in palliative therapy.^(3, 4, 9)

Recommendation 5

Treatment: Pharmacological

Bisphosphonates:

- Bisphosphonates are appropriate to administer when serum calcium (corrected) is greater than or equal to 3 mmol per litre or when serum calcium (corrected) is less than 3 mmol per litre when accompanied by symptoms.⁽³⁾

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- Bisphosphonates cause a fall in calcium in 48 hours.⁽⁹⁾ These agents are very useful and well tolerated but are quite expensive.⁽¹⁾
- Oral bisphosphonates (like clodronate or alendronate) can be used, but in many palliative care patients are not well tolerated. Parenteral drugs including pamidronate and zoledronic acid have been used with success⁽⁸⁾ and are better tolerated and more effective than oral.⁽⁵⁾
- Do not give bisphosphonates until the patient is fully re-hydrated and has an adequate urine output.⁽⁴⁾
- Recheck serum calcium, electrolytes, urea, and creatinine on the 3rd day after administering bisphosphonates.⁽¹⁾
- Renal failure is the most serious adverse effect.⁽³⁾ Bisphosphonates are contraindicated in patients with serum creatinine greater than 400 μmol per litre or calculated creatinine clearance of less than 10 mL per minute.⁽³⁾
- In patients with pre-existing renal disease and a serum creatinine less than 265 μmol per litre, no change in dosage, infusion time or interval of pamidronate is required for multiple myeloma patients.⁽¹²⁾
- Caution is required in patients receiving other drugs that may affect renal function (NSAIDS, ACE inhibitors, aminoglycosides).⁽³⁾
 - **Pamidronate** 30 to 90 mg I.V. for severely elevated calcium (over 3.5 mmol per Litre) use 90 mg I.V. bolus in 250 mL^(13, 14) to 500 mL NS^(4, 10) over 60^(13, 14) to 90 minutes.^(2, 9)
 - Pamidronate has been shown to be superior to clodronate in terms of duration of normal calcium levels achieved.^(2, 9)
 - Best given with acetaminophen, 500 mg PO or rectally to prevent pamidronate fever.⁽⁴⁾
 - Usual expected duration of effect of pamidronate is 3 to 4 weeks.^(1,3)
 - **Clodronate** 1500 mg I.V. over 4 hours in 250 or 500 mL NS^(1, 3, 10) or 500 mg I.V. daily for 3 days – dilute in 500 cc NS.
 - Usual expected duration of action of clodronate is 2 weeks.^(1, 3)
 - Dose adjustment for decreased renal function: if creatinine clearance is 10 to 50 mL per minute a dose reduction of 25% to 50% is recommended.⁽³⁾
 - **Zoledronic acid** 4 mg in 100 mL NS over 15 minutes I.V.^(1, 2, 9, 12) Zoledronic acid has been shown to achieve normal serum calcium levels in more patients, faster and with longer duration than Pamidronate.⁽⁹⁾
 - Usual expected duration of effect of zoledronic acid is 4 to 6 weeks.⁽¹⁾
 - Useful for refractory hypercalcemia treatment.⁽¹⁾
 - Fever is a common side effect of zoledronic acid, with renal impairment seen rarely.⁽⁵⁾

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- Zoledronic acid has been found to be effective in reducing and delaying bone complications across a broad range of solid tumours and multiple myeloma.⁽²⁾
- Dose adjustment for decreased renal function:⁽³⁾

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid Recommended Dose
Greater than 60	4 mg
50 to 59	3.5 mg
40 to 49	3.3 mg
30 to 39	3 mg

Calcitonin:

- Calcitonin 4 to 8 international units per kg given S.C. or I.M. q12h (can titrate up to q6h).^(3, 4, 16)
- Calcitonin has a rapid onset of action – approximately 4 hours⁽⁹⁾ but has a shorter duration of action⁽⁴⁾ and is very useful when a rapid lowering of serum calcium is required^(1, 3-5, 16) but needs to be combined with bisphosphonates.^(3, 5, 16)
- Possible side effects: flushing, mild nausea, crampy abdominal pain.⁽⁴⁾ A small risk of hypersensitivity exists due to salmon derivation.⁽³⁾

Steroids:

- Corticosteroids may lower serum calcium if they have an antineoplastic effect on the underlying malignancy.⁽³⁾ They should be reserved for situations in which bisphosphonates are not easily accessible or are ineffective or in which other indication for corticosteroids (pain or nausea) exist.⁽³⁾
- Prednisone 40 to 100 mg daily⁽⁹⁾ for up to one week.⁽⁴⁾
- Hydrocortisone 100 mg I.V. q6h.⁽⁷⁾
- Dexamethasone 4 mg S.C. q6h for 3 to 5 days.
- Steroids are particularly useful for hypercalcemia seen with lymphomas and multiple myeloma.⁽⁵⁾

Drugs promoting hypercalcemia (thiazide diuretics, lithium, ranitidine, cimetidine, vitamins A and D and preparations containing calcium) should be withdrawn.^(4, 9, 15)

The routine use of furosemide in conjunction with hydration to promote calcium excretion is not recommended, because of the risk of volume and electrolyte depletion.⁽³⁾

References

Information was compiled using the CINAHL, Medline (1996 to April 2006) and Cochrane, DSR, ACP Journal Club, DARE and CCTR databases, limiting to reviews/systematic reviews, clinical trials, case studies and guidelines/protocols using hypercalcemia terms in conjunction with palliative/hospice/end of life/dying. Palliative care textbooks mentioned in generated articles were hand searched. Articles not written in English were excluded.

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