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Clinical Practice Guideline

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OXFORD

Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline

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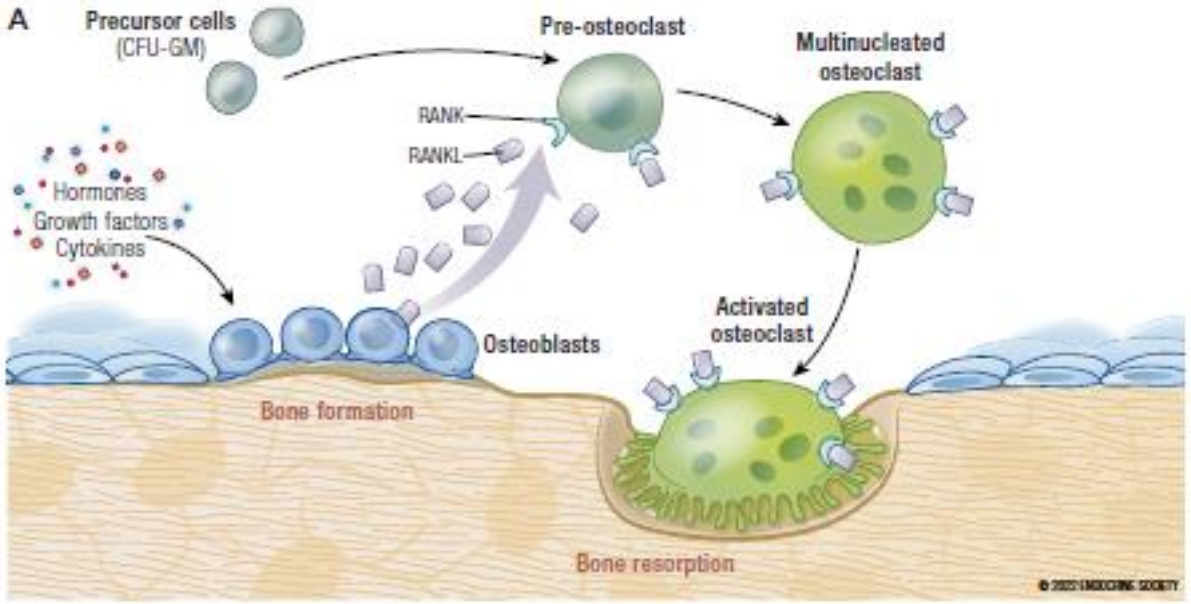
“Introduction”

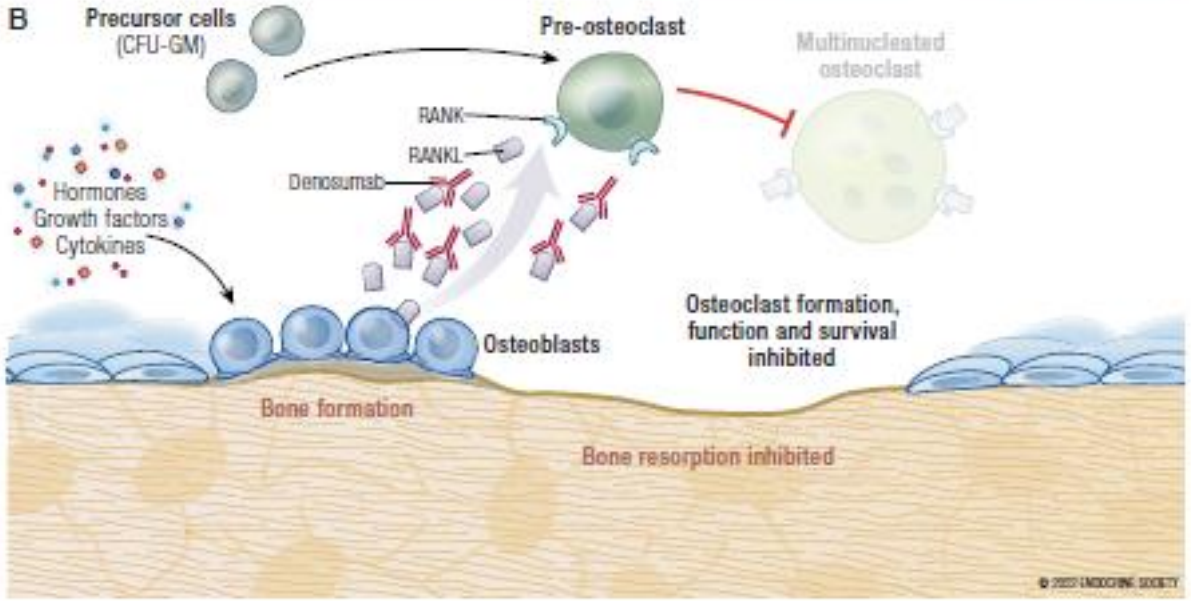
Overview of Hypercalcemia of Malignancy (HCM)

- Hypercalcemia of malignancy (HCM) is **the most common metabolic complication** of cancer and carries significant morbidity and mortality.
- Its prevalence ranges from 2% to 30% depending on **cancer type and disease stage**. HCM occurs most frequently in **solid tumors** such as breast, lung, and renal cancers, as well as multiple myeloma.
- Clinical manifestations are nonspecific and depend on **calcium level, its rate of rise**, and the **presence of bone metastases**.
- Severity is typically categorized as mild, moderate, or severe **based on serum calcium thresholds.**

Pathophysiology of HCM

- It addresses **humoral** and **osteolytic HCM**, **myeloma-associated hypercalcemia**, **calcitriol-mediated forms**, and **hypercalcemia from parathyroid carcinoma**.
- A large proportion of hypercalcemia of malignancy (HCM) cases are linked to **parathyroid hormone–related peptide (PTHrP).**
- PTHrP stimulates osteoclast differentiation and activity, causing **bone resorption** and **calcium release into bloodstream**.
- This process occurs without bone metastases and is driven by the RANK–RANKL signaling system.
- Osteoclast activation plays a central role in skeletal calcium release—key to understanding HCM's humoral mechanism.





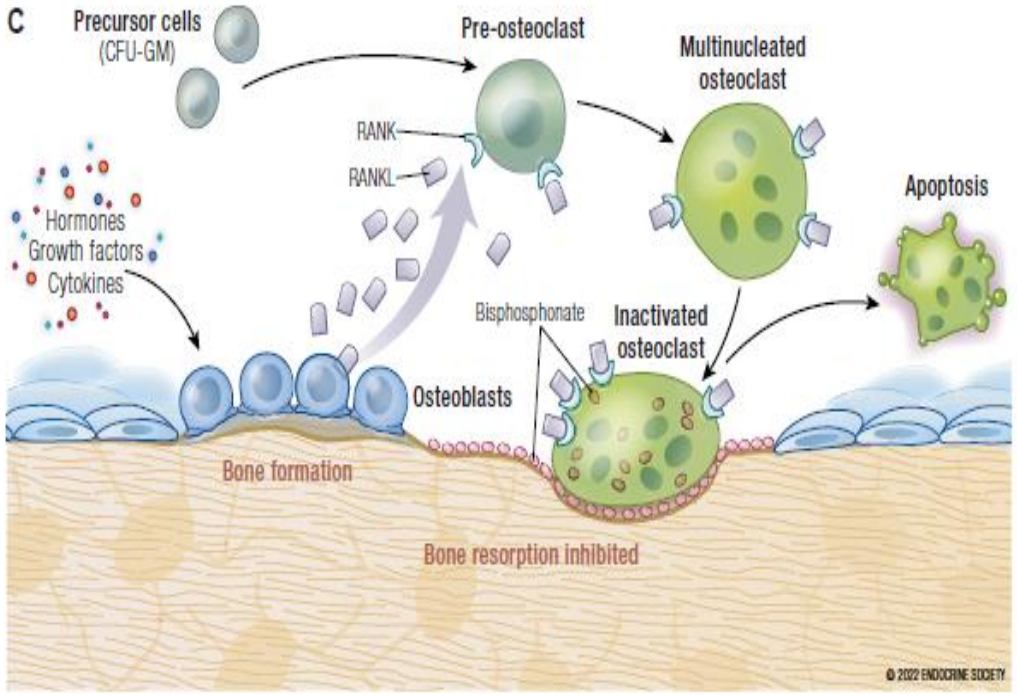


Figure 1. Osteoclast formation, activity, and pharmacologic inhibition. (A) Osteoclasts develop from osteoclast precursor cells when receptor activator of nuclear factor κ B (RANK) ligand (RANKL), produced by osteoblasts, binds to the receptor RANK on pre-osteoclasts. Multinucleated osteoclasts adhere to bone where they undergo differentiation into mature activated osteoclasts which resorb bone. (B) Denosumab is a humanized monoclonal antibody that binds to RANKL to block RANK:RANKL binding, resulting in inhibition of osteoclast formation, function, and survival. (C) Bisphosphonates adhere to the mineral component of bone. During the resorptive process, mature osteoclasts endocytose bisphosphonates, resulting in osteoclast inactivation and apoptosis. Abbreviation: CFU-GM, colony forming unit granulocyte–macrophage. Adapted from Boyle WJ, Simonet WS, Lacey DI. *Nature*. 2003;423(6937):337-342. (24)

Clinical Manifestations and Impact

- Mild hypercalcemia may produce symptoms such as **fatigue, constipation, and cognitive difficulties.**
- Moderate to severe elevations, or rapid calcium increases, can lead to **polyuria, polydipsia, and renal failure.** High calcium levels are associated with **poorer quality of life**, **increased hospitalization**, and **higher mortality.**
- Earlier studies reported 30-day mortality **rates approaching 50%,** though outcomes have improved with modern therapies.
- Effective treatment of the **underlying malignancy** remains essential for long-term control and prevention of recurrence.

Appendix A: Common Terminology Criteria for Adverse Events Grade[1]

Grade based on severity	Corrected serum calcium
Grade 1	Corrected SCa of >ULN to 11.5 mg/dL (2.9 mmol/L); ionized calcium >ULN to 1.5 mmol/L
Grade 2	Corrected SCa of >11.5 to 12.5 mg/dL (2.9 to 3.1 mmol/L); ionized calcium >1.5 to 1.6 mmol/L; symptomatic
Grade 3	Corrected SCa of >12.5 to 13.5 mg/dL (3.1 to 3.4 mmol/L); ionized calcium >1.6 to 1.8 mmol/L; hospitalization indicated
Grade 4	Corrected SCa of >13.5 mg/dL(3.4 mmol/L); ionized calcium >1.8 mmol/L; life-threatening consequences

- Common Terminology Criteria for Adverse Events (CTCAE) grade classifies HCM into 4 grades based on corrected serum calcium (corrected SCa).
- ULN = upper limit of normal (10.8 mg/dL).
- "Corrected calcium" may lead to confusion that the result is due to error and shall be corrected. So, the term "adjusted" calcium is preferred over "corrected" calcium.[2]
- Adjusted total calcium (mg/dL) = total calcium (mg/dL) + 0.8 [4 – albumin(g/dL)] or adjusted total calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)].[2,3]

[1]CTCAE, US Department of Health and Human Services. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published: November 27, 2017. (86)
[2]Fraser, William D. (2018). 63. Bone and Mineral Metabolism. In Rifai, Nader. Tietz textbook of clinical chemistry and molecular diagnostics. St. Louis, Missouri: Elsevier. (87)
[3]Maier JD,Levine SN (2015). "Hypercalcemia in the Intensive Care Unit: A Review of Pathophysiology, Diagnosis, and Modern Therapy." *J Intensive Care Med*. 30(5):235-252. (88)

Principles of HCM Management

- Management focuses on **correcting hypovolemia**, **enhancing renal calcium excretion**, and **reducing bone resorption**.
- **Hydration** is the first-line therapy due to its rapid effect, and **loop diuretics like furosemide** may be used selectively, though supporting evidence is limited.
- **Calcitonin** offers rapid onset of calcium reduction and is often combined with potent antiresorptives. **Bisphosphonates** and **denosumab** serve as primary agents for suppressing bone resorption in most cases.
- Additional treatments include **glucocorticoids for calcitriol-mediated HCM and calcimimetics** for parathyroid carcinoma.

Antiresorptive Therapies

- **Two major classes of antiresorptive agents reduce osteoclast activity:**

  1. Denosumab (Dmab) – a monoclonal antibody targeting RANKL, blocking osteoclast formation.

  2. Bisphosphonates (BPs) – act on mature osteoclasts, inducing their apoptosis.

- **- Both have been proven in placebo-controlled trials leading to regulatory approval.**

  - No study has yet directly compared BPs vs Dmab efficacy in adults with HCM.

  - Rebound hypercalcemia may occur after discontinuing Dmab in metastatic cancer patients.

Table 1. Treatment regimens for hypercalcemia of malignancy

Table 1. Continued

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
	osteoclast surfaces) and prevents osteoclast formation and thus bone resorption.			discontinuation. Patients with GFR < 30 mL/ min have a higher risk of hypocalcemia, and a lower dose should be considered.
Calcimimetics Oral: Initial: 30 mg twice daily; increase dose incrementally every 2 to 4 weeks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) as necessary to normalize SCa levels.	Calcium-sensing receptor agonist, reduces parathyroid hormone secretion, and may decrease renal calcium reabsorption.	2 to 3 days	During therapy. Reduces calcium by at least 1 mg/dL (0.25 mmol/L) in approximately 60% of patients.	Nausea, vomiting, headache, and fractures. Case reports indicate reduction of calcium levels in patients with refractory HCM related to non–small-cell lung, neuroendocrine, breast, or renal cancer.

Source: Information on mode of action, onset of action and duration of effect obtained in part from Lexicomp© Copyright 1978-2021, or relevant papers cited from Chakhtoura M, El-Hajj Fuleihan G. *Endocrinol Metab Clin North Am,* 2021; *50*(4): 781-792 (15) and Guise T and Wysolmerski J. *N Engl J Med,* 2002;386:1443-1451. (16).

Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; ONJ, osteonecrosis of the jaw; RANK, receptor activator of nuclear factor κ-B; RANKL, receptor activator of nuclear factor κ-B ligand; SQ, subcutaneous.

*Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

Table 2. Ungraded good practice statements

Ungraded good practice statement (UGPS) definition: Necessary actionable and clear guideline statements that are supported only by overwhelming indirect evidence. The supporting direct evidence is either unavailable or considered inappropriate for a systematic review process. UGPS should describe the population and intervention options and, if appropriate, comparator components of the recommendation (28, 29).
The panel reviewed the criteria for UGPSs and makes the following UGPSs for patients with HCM:
UGPS 1: In adults with HCM, adequate hydration with intravenous (IV) fluids is first-line therapy while awaiting the effect of antiresorptive drugs. Therapy should be tailored according to cardiac function.
UGPS 2: In adults with HCM, dental hygiene and oral health, including visual examination of the mouth, should be monitored in the context of the provision of antiresorptive therapy.
UGPS 3: To avoid hypocalcemia in adults with HCM who receive antiresorptive therapy, vitamin D levels should be monitored and managed in accordance with Endocrine Society vitamin D guidelines. These guidelines are however not specific to patients with HCM.
UGPS 4: In adults with HCM, renal function (creatinine clearance or estimated glomerular filtration rate [eGFR]) should be assessed prior to administration of IV BPs.
UGPS 5: In adults with HCM and renal insufficiency (defined as creatinine clearance <60 mL/min) who are treated with IV BPs, administer renal BP dosing of zoledronic acid over 30 to 60 minutes or renal BP dosing of pamidronate over 2 to 24 hours.
UGPS 6: In adults with HCM, serum magnesium and phosphorous levels should be monitored and repleted if determined to be low.
UGPS 7: In adults with HCM, clinical oncology consultation for treatment of the underlying malignancy should be undertaken.
UGPS 8: In adults with hypercalcemia due to parathyroid carcinoma, surgical consultation should be pursued for definitive treatment.

Question 1:

Should a bisphosphonate or denosumab vs no treatment with these agents be used for adults with hypercalcemia of malignancy?

- **Recommendation 1:**

✓ **n adults with hypercalcemia of malignancy (HCM), we recommend treatment with an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (1⊕OOO)**

Evidence on Bisphosphonate Efficacy

- Four published trials evaluated the ***efficacy of bisphosphonates (BPs) versus placebo in treating HCM.**
- **The BPs studied included etidronate (2 trials), clodronate, and pamidronate.**
  One trial (Rotstein et al.) enrolled only breast cancer patients, while the other three included HCM from any malignancy type.
- **In pooled analyses, 61.3% of BP-treated patients achieved resolution of HCM, compared with 27.5% in the placebo groups.**
- **This corresponds to a rate ratio (RR) of 2.22 (95% CI 1.57–3.14), indicating significantly greater efficacy with BPs.**

Role of Standard Care and Calcium Changes

- In all four trials, patients received standard care of that era, including intravenous fluid hydration.
- IV hydration was used to improve renal perfusion and promote calciuria, contributing to lower serum calcium levels.
- The placebo groups also showed significant declines in serum calcium (SCa) due to hydration alone. However, the reduction in SCa was greater and more clinically meaningful when BPs were added to IV fluids.

Harms and Adverse Events of Bisphosphonates

- In the analysis by Singer et al., mortality was higher in BP-treated patients, but the difference was **not statistically significant** (RR 1.52; 95% CI 0.91–2.53).
- Adverse events were more frequent with BP therapy (RR 2.33; 95% CI 1.16–4.69). Common adverse events included **fever, infusion-site reactions, hypophosphatemia, hypocalcemia, nausea, diarrhea, and taste disturbances.**

Other Evidence-to-Decision Criteria (Beyond the 4 Trials)

- 3/4 included trials used early-generation BPs (etidronate, clodronate) that lack a nitrogen moiety → less potent than nitrogen-containing BPs (e.g., pamidronate).
- Etidronate and clodronate are not approved by the FDA (or other regulators) for HCM.
- Pamidronate is approved worldwide for HCM.

Justification for the Strong Recommendation (GRADE)

- - When the evidence quality is low, but the potential benefit in a life-threatening situation is meaningful, a strong recommendation may be warranted.
  - Hypercalcemia of malignancy (HCM) is often life-threatening.
  - Therefore, the panel considered the severity/urgency of the condition a key factor supporting the strength of the recommendation.
  - The panel concluded the balance of effects likely favors the intervention.
  - Although resources, cost-effectiveness, and equity may vary, treatment is expected to be feasible and accessible.

Appendix B: Summary of Evidence to Decision Judgements for all Recommendations

PICO question	Values	Balance of effects	Resources required	Cost-effectiveness	Equity	Accessibility	Feasibility	Recommendation strength and direction
1. Should a bisphosphonate or denosumab vs no treatment with a bisphosphonate or denosumab be used for adults with hypercalcemia of malignancy?	Probably no important uncertainty or variability	Probably favors intervention	Varies	Varies	Varies	Probably yes	Probably yes	Strong recommendation, very low certainty of evidence (1⊕OOO)

Question 2:

Should denosumab be used instead of a bisphosphonate for adults with hypercalcemia of malignancy?

Recommendation 2:

- **In adults with hypercalcemia of malignancy (HCM), we suggest treatment with denosumab (Dmab) over an intravenous (IV) bisphosphonate (BP). (2⊕OOO)**

(Benefits)

1. No prospective studies directly evaluated whether ***BP vs denosumab resolves HCM as an endpoint.**
2. **The SR identified 5 phase 3 trials in solid tumors/multiple myeloma with bone metastases, randomized to monthly zoledronic acid (4 mg) vs denosumab (120 mg).**
3. **Most studies assessed SREs (e.g., pathologic fracture, radiation/surgery to bone, spinal cord compression) and not HCM resolution.**

(Harms & Net Impact)

- **Findings suggested lower incidence of HCM with denosumab (1.7%) vs zoledronic acid (3.5%) (Stopeck et al).**
- **- Denosumab also reduced recurrent HCM risk by 52%.**
  - Denosumab showed fewer SREs, but was associated with more hypocalcemic events than IV bisphosphonates.
  - Overall survival was not different between groups in the included studies.

Recommendation Basis & Practical Considerations

- **Based on very low certainty evidence, the panel suggests denosumab over IV bisphosphonates for adults with HCM.**
- **Although the panel judged hypocalcemia as not an outcome priority, clinicians should remain vigilant—especially with vitamin D deficiency or renal insufficiency.**
- **Overall, the balance of effects probably favors denosumab; feasibility and access are likely***, though resources and cost-effectiveness may vary (Appendix B).

Appendix B: Summary of Evidence to Decision Judgements for all Recommendations

PICO question	Values	Balance of effects	Resources required	Cost-effectiveness	Equity	Accessibility	Feasibility	Recommendation strength and direction
2. Should denosumab vs a bisphosphonate be used for adults with hypercalcemia of malignancy?	Probably no important uncertainty or variability	Probably favors intervention	Varies	Varies	Varies	Probably yes	Probably yes	Conditional recommendation, very low certainty evidence (2⊕OOO)

Question 3:

Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will start bisphosphonate or denosumab?

- **Recommendation 3:**
- In adults with severe hypercalcemia of malignancy (HCM) (serum calcium [SCa] > 14 mg/dL [3.5 mmol/L]), we suggest a **combination of calcitonin and an intravenous (IV) bisphosphonate (BP) or denosumab** (Dmab) as initial treatment compared with only intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⨁OOO)
- ***Remark*** **Calcitonin treatment should be limited to 48 to 72 hours due to tachyphylaxis**

(Benefits & Resolution)

- The SR identified ***one retrospective comparative analysis (total 140 patients) treated for moderate–severe HCM with IV bisphosphonate (BP) and/or calcitonin.**
  - **Despite higher initial calcium in the combination group, calcium levels at 24, 48, and 72 hours were similar.**
- **HCM resolution:**
  - **IV BP only: 69/94**
  - **IV BP + calcitonin: 28/46**
  - **Effect estimate: RR 1.21 (95% CI 0.93 to 1.57)**

Harms & Safety (Mortality & Hypocalcemia)

- **Mortality was lower in the BP-only group: RR 0.45 (95% CI 0.22 to 0.91)**
- **Hypocalcemia adverse events:**
  - **IV BP: 5/94**
  - **IV BP + calcitonin: 1/46**
  - **Incident rate ratio: 0.49 (95% CI 0.14 to 1.69)**

Recommendation Basis & Uncertainty

- **The panel had concern about increased mortality in the calcitonin + BP group, but noted it may reflect:**

  chance, or more severe baseline illness in the combination group.

- **Therefore, the panel judged the balance of effects as "don't know".**

- **Calcitonin cost has increased, making it extremely expensive in the United States.**

- **In severe HCM (and possibly renal dysfunction), calcitonin plus IV fluids may be considered while awaiting effects of more potent antiresorptives (BP or Dmab*).**

Appendix B: Summary of Evidence to Decision Judgements for all Recommendations

PICO question	Values	Balance of effects	Resources required	Cost-effectiveness	Equity	Accessibility	Feasibility	Recommendation strength and direction
3. Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will be started on a bisphosphonate or denosumab?	Probably no important uncertainty or variability	Don't know	Moderate costs	No included studies	Varies	Probably yes	Probably Yes	Conditional recommendation, very low certainty evidence (2⊕OOO)

“Refractory and Recurrent Hypercalcemia”

Background (Why sequencing matters)

- ***IV fluids + calcitonin + IV BPs or Dmab can effectively manage HCM.**
- **IV BPs are standard for moderate–severe/symptomatic HCM, but some patients develop rapid recurrence or become refractory, often in progressive cancer.**
- **Dmab is effective for BP-refractory HCM (open-label phase 2: Ca to target within 10 days; median response 104 days).**
- **No studies directly compare sequence: IV BP → Dmab vs Dmab → IV BP.**

Question 4:

Should denosumab vs no denosumab be used for adults with refractory or recurrent hypercalcemia of malignancy already receiving bisphosphonates?

▶ Recommendation 4:

- ✓ **In adults with refractory/recurrent hypercalcemia of malignancy (HCM) on an intravenous (IV) bisphosphonate (BP), we suggest the use of denosumab (Dmab) compared with management without (denosumab) Dmab. (2⊕OOO)**

Benefits & Harms (What evidence exists)

- S.R found 3 publications (44 patients) **indirectly addressing** sequencing IV BP exposure → Dmab.
- Evidence suggests Dmab lowers SCa in patients with HCM after BP exposure (BP-refractory context).
- **Reported Dmab toxicities**: hypocalcemia and hypophosphatemia.
- **Outcomes considered key**: resolution of HCM and mortality reduction.

Decision basis (Uncertainty & feasibility)

- No evidence identified for patients with HCM refractory to Dmab who then received IV BPs.
- **Evidence supports resolution for IV BP → Dmab, not the comparator.**
- **Panel conclusion:** balance of effects = unknown, with variability in resources, cost-effectiveness, equity; but treatment is probably feasible and accessible*.

“Hypercalcemia Due to Calcitriol-Associated Malignancy”

Background: Calcitriol-Mediated HCM

- Ectopic calcitriol production (less common HCM cause, almost exclusive to lymphomas).
- Mechanism: **Increased calcium & phosphorus absorption (GI tract) + increased bone resorption (osteoclasts).**
- Worse progression-free survival in **non-Hodgkin lymphoma** patients with elevated calcitriol (potential marker of advanced disease).
- **Glucocorticoids:**
  - Interfere with GI calcium absorption.
  - Inhibit 1-α-hydroxylase (limits calcitriol conversion from 25-hydroxyvitamin D).
  - Dietary calcium restriction is also crucial.
  - Continued hypercalcemia is common despite glucocorticoid treatment.

Question 5:

Should a bisphosphonate or denosumab vs no bisphosphonate or denosumab be used for adults with hypercalcemia resulting from tumors associated with high calcitriol levels who are already treated with a glucocorticoid?

- **Recommendation 5:**

✓ **In adults with hypercalcemia of malignancy (HCM) from tumors associated with high calcitriol levels, such as lymphomas, who are already receiving glucocorticoid therapy but who continue to have severe or symptomatic hypercalcemia, we suggest the addition of an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)**

Benefits & Harms: Limited Direct Evidence

- No direct evidence on BP or Dmab for calcitriol-mediated HCM already on glucocorticoids (but still severe/symptomatic).
- Indirect evidence: 4 RCTs (patients with HCM responding to IV BP therapy) showed benefit (RR 2.22; 95% CI: 1.57 to 3.14).
- **Panel conclusion on desirable effects: Undetermined due to evidence indirectness.**

Decision Basis & Future Research

- **Antiresorptive medications (IV BPs & Dmab): Effective at inhibiting osteoclast-mediated bone resorption from excess calcitriol.**

  Panel conclusion: Balance of effects, resources, cost-effectiveness, equity = varied, but treatment likely feasible and accessible.

- **- Increased risk of ONJ/atypical femoral fractures*** with BPs/Dmab in patients on high-dose glucocorticoids (though overall risk is low).

“Adults With Hypercalcemia Due to Parathyroid Carcinoma”

Background: Parathyroid Carcinoma & Why Medical Therapy

- Parathyroid carcinoma **is rare** (<1% of primary hyperparathyroidism cases).
- Symptoms at diagnosis are usually **moderate to severe hypercalcemia.**
- **Surgery** (parathyroidectomy) should be considered if feasible, but is often not possible.
- Recurrence **occurs in >50%,** typically with progressive Ca increase → medical management is often needed.
- **Cinacalcet** approved (FDA/EMA) for HCM due to parathyroid carcinoma; lowers Serum Ca but GI adverse events may limit full dosing.
- **Zoledronic acid** (IV BP) approved worldwide for HCM; **Dmab** approved in many countries for the same indication.

Question 6:

Should a calcimimetic vs a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma?

Recommendation 6:

- ✓ **In adult patients with hypercalcemia due to parathyroid carcinoma, we suggest treatment with either a calcimimetic or an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)**

Remarks:

- ✓ **Surgery should always be considered in parathyroid carcinoma once severe hypercalcemia is stabilized. Medical therapy serves as a bridge to surgical management but is not a replacement for it.**
- ✓ **If hypercalcemia is moderate to severe, starting with IV bisphosphonate or denosumab is preferred to achieve faster normalization.**
- ✓ **Calcimimetics are more suitable for stable patients with mild hypercalcemia.**
  IV BP and Dmab often show quicker onset and better tolerability compared with escalating calcimimetic doses.

Benefits & Harms: Evidence is Indirect / Low Certainty

- **SR found 5 studies (indirect evidence).**

  - Oral BP vs placebo (2 RCTs): alendronate did not significantly improve hypercalcemia resolution

  - OR 1.13 (95% CI 0.07–18.75)

  - Cinacalcet in observational studies (3 studies): SCa normalized in 14/43

- **After cinacalcet and/or BPs fail (case series + case reports, 19 patients, 11 with carcinoma):**

1. ***Dmab led to resolution in 11 patients (8 with carcinoma)***
2. ***Durable resolution reported in 5 patients, lasting 2–14 months***
3. **Mortality:**

   - 2 observational studies: 8/46 died on cinacalcet

   - No deaths judged treatment-related

Question 7:

Should addition of a bisphosphonate or denosumab vs no addition be used for adults with parathyroid carcinoma inadequately controlled on a calcimimetic?

- **Recommendation 7:**

✓ **In adult patients with hypercalcemia due to parathyroid carcinoma not adequately controlled despite treatment with a calcimimetic, we suggest the addition of an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an IV BP or Dmab. (2⊕OOO)**

Benefits & Harms (Evidence for adding IV BP or Dmab to cinacalcet)

- **No direct studies addressing this question.**
- ***Panel used 1 retrospective study as indirect evidence (Eremkina et al., 10 patients; 2 with parathyroid carcinoma):***

  - Cinacalcet 30–120 mg before admission → no significant SCa change

  - All received a single 60 mg Dmab + isotonic saline; 8 continued cinacalcet 30–60 mg
- ***Normocalcemia in 4/10:***

  - 1 after 3 days

  - 3 after 9 days

Other Evidence-to-Decision (EtD) Considerations

- **Adding IV BP or Dmab to cinacalcet may:**
  - improve HCM control
  - enable lower cinacalcet dosing or withdrawal
  - yield a better risk/benefit balance
  - potentially reduce hospitalization and total cost
- **Acceptability/feasibility**
  - Dmab: easier administration (subcutaneous) and less renal monitoring
  - IV BPs: may worsen renal function
  - therefore Dmab favored in patients with HCM + renal insufficiency

Question 8:

Should a calcimimetic vs no calcimimetic be used for adults with hypercalcemia due to parathyroid carcinoma who are not adequately controlled with a bisphosphonate or denosumab?

- **Recommendation 8:**

✓ **In adult patients with hypercalcemia due to parathyroid carcinoma who are not adequately controlled on an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) therapy, we suggest the addition of a calcimimetic compared with management without a calcimimetic. (2⊕OOO)**

Benefits and Harms (Evidence Overview)

- **The systematic review found no studies comparing calcimimetics with placebo in patients with HCM due to parathyroid carcinoma who had already received bisphosphonates or denosumab.**
- **Two single-arm studies evaluated the effect of cinacalcet on serum calcium levels in this population.**
  In the study by Silverberg et al., 29 patients with parathyroid carcinoma were treated, including 23 who had previously received bisphosphonates.
- **All patients had undergone prior neck resection before enrollment.**
  The primary endpoint was a reduction of at least 1 mg/dL (0.25 mmol/L) in serum calcium.
  Eighteen patients (62%) achieved the primary endpoint, with a mean reduction of 1.7 mg/dL (0.425 mmol/L).
- **Fractures occurred in six patients, and common adverse effects included nausea, vomiting, dehydration, and headache.**

Justification for the Recommendation

- **The panel judged the overall certainty of evidence to be very low.**
  There is a lack of high-quality comparative studies evaluating important clinical outcomes.
- **Despite these limitations, the panel concluded that the balance of benefits and harms probably favors treatment.**
- **Resource use was considered potentially moderate depending on the healthcare setting.**
- **Patients with parathyroid carcinoma often require higher doses of cinacalcet.**
  Doses may reach the maximum approved level of 360 mg per day.

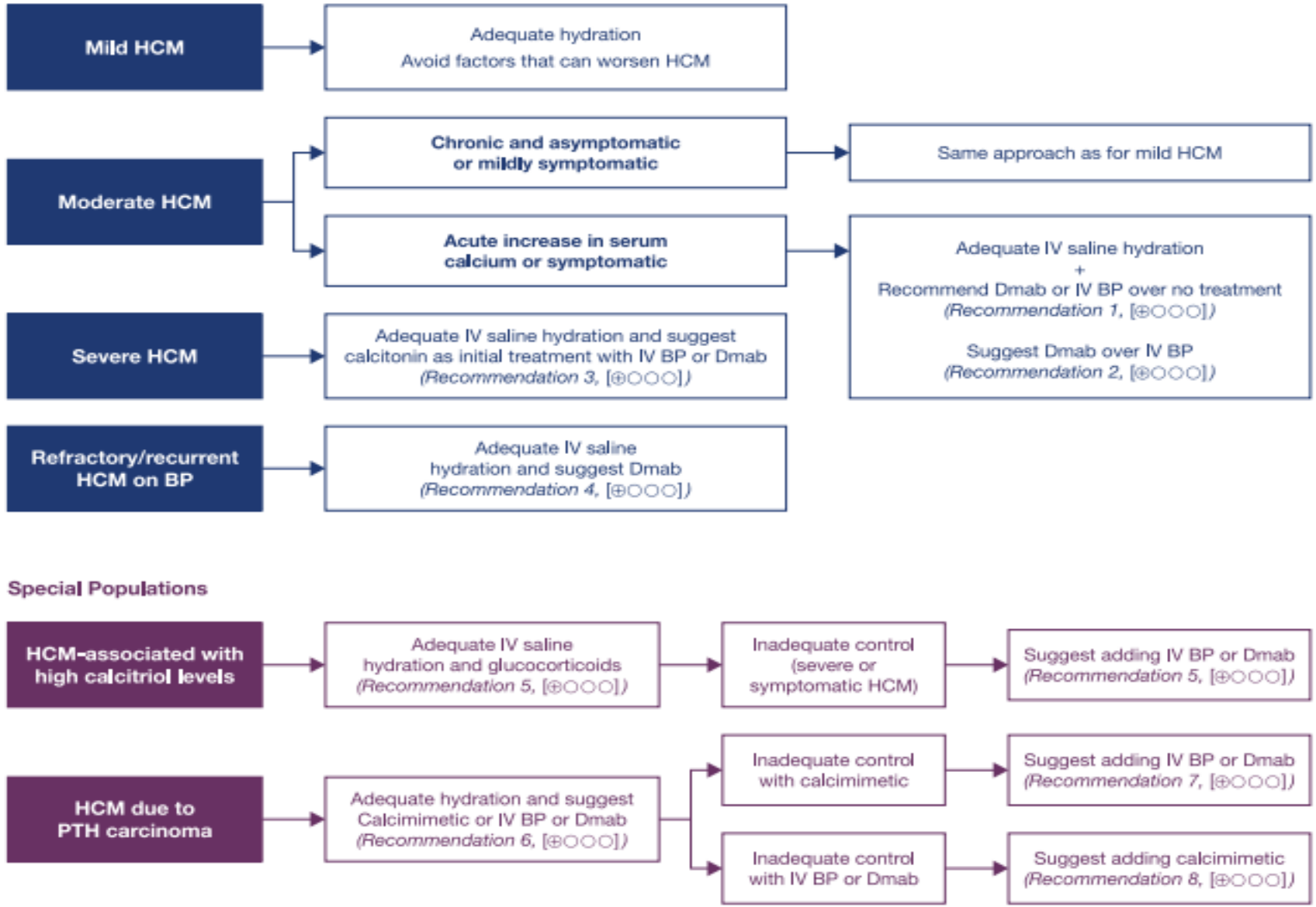


Figure 2. Suggested workflow for the management of HCM. The therapeutic approach depends upon the pathophysiology and severity of hypercalcemia and the rapidity of serum calcium increase. The severity of hypercalcemia is classified as the following: mild, albumin-adjusted SCa < 12 mg/dL (<3 mmol/L); moderate, albumin-adjusted SCa 12 to 14 mg/dL (3 to 3.5 mmol/L; Severe, albumin-adjusted SCa > 14 mg/dL; (>3.5 mmol/L). The ungraded good practice statements are listed below (see Table 2) and various recommendations are detailed in the main text. *Refer to the full EtDs and recommendations for additional considerations behind the recommendations. Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; Dmab, Denosumab; IV BP, intravenous bisphosphonate; SCa, serum calcium.