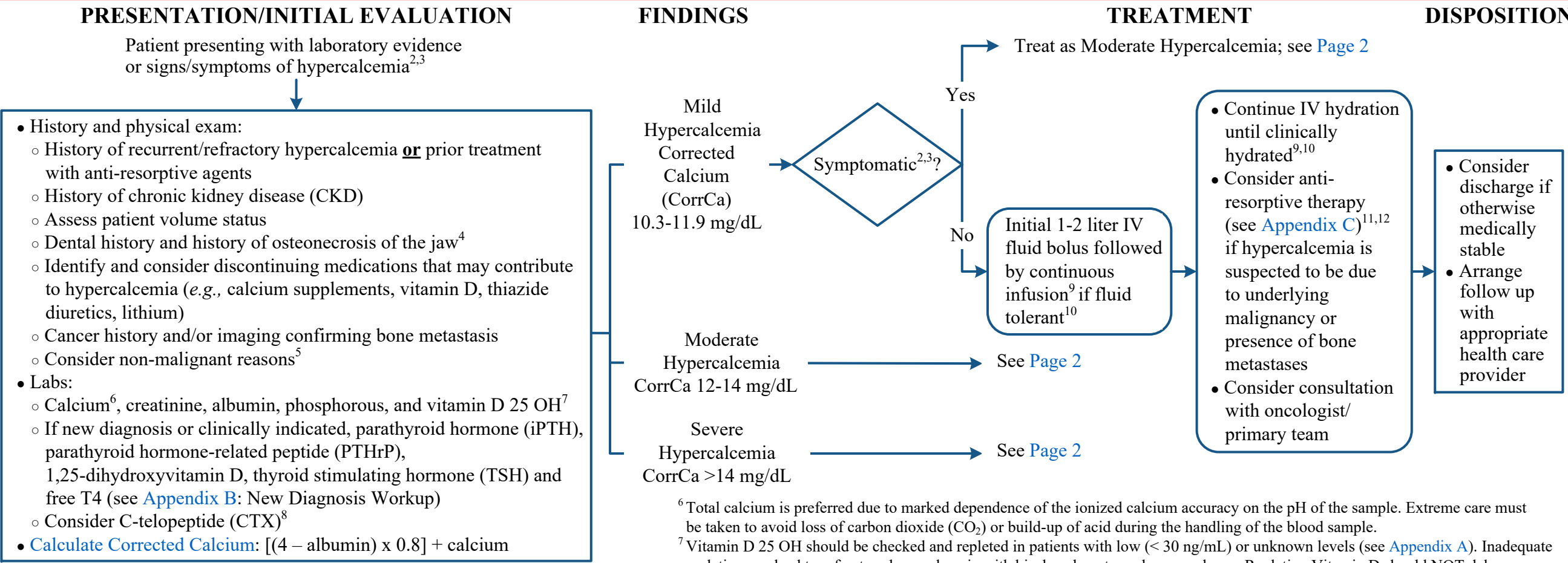


Acute Hospital Management of Hypercalcemia¹

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.



¹ Includes patients being treated in the Acute Cancer Care Center (ACCC), Clinical Decision Unit (CDU), and Urgent Symptom Clinic (USC)

² Mild symptoms include constipation, confusion, nausea, abdominal pain, acute kidney injury (increase in creatinine of ≥ 0.3 mg/dL), fatigue, polyuria, and polydipsia

³ Severe symptoms include severe altered mental status, obtundation, stupor, coma, lethargy, obstipation, intractable nausea/vomiting, seizures, and EKG changes

⁴ In patients with a history of osteonecrosis of the jaw or markedly poor dentition, zoledronic acid, pamidronate and denosumab use should be avoided unless benefit outweighs risk. Consider Endocrinology or Dental Oncology consult.

⁵ Non-malignant reasons to consider include: hyperparathyroidism, milk alkali, medication-induced, immobilization, granulomatous disorders, hormonal disorders (adrenal, thyroid, etc.)

⁶ Total calcium is preferred due to marked dependence of the ionized calcium accuracy on the pH of the sample. Extreme care must be taken to avoid loss of carbon dioxide (CO₂) or build-up of acid during the handling of the blood sample.

⁷ Vitamin D 25 OH should be checked and repleted in patients with low (< 30 ng/mL) or unknown levels (see [Appendix A](#)). Inadequate repletion can lead to refractory hypocalcemia with bisphosphonate or denosumab use. Repleting Vitamin D should NOT delay treatment of hypercalcemia.

⁸ Consider baseline fasting CTX and repeat as clinically indicated to assess anti-resorptive treatment response

⁹ Initial 1-2 liter IV bolus followed by continuous infusion of 100-200 mL/hour until clinically hydrated based on physical assessment and available lab values. Non-calcium containing IV fluids are recommended (e.g., isotonic saline solutions, Plasma-Lyte).

¹⁰ IV fluids should be used judiciously in patients predisposed to fluid overload (e.g., heart failure, advanced chronic kidney disease, ascites, anuric acute kidney injury, etc.) and should be guided by physical exam, laboratory findings, and imaging. Consider loop diuretics as needed to maintain fluid balance.

¹¹ Risk of renal toxicity may be higher with bisphosphonates in the setting of dehydration. Adequate hydration is recommended prior to drug administration.

¹² See [Appendix D](#) for drug information and formulary restrictions, dosing considerations, contraindications and adjunctive therapies

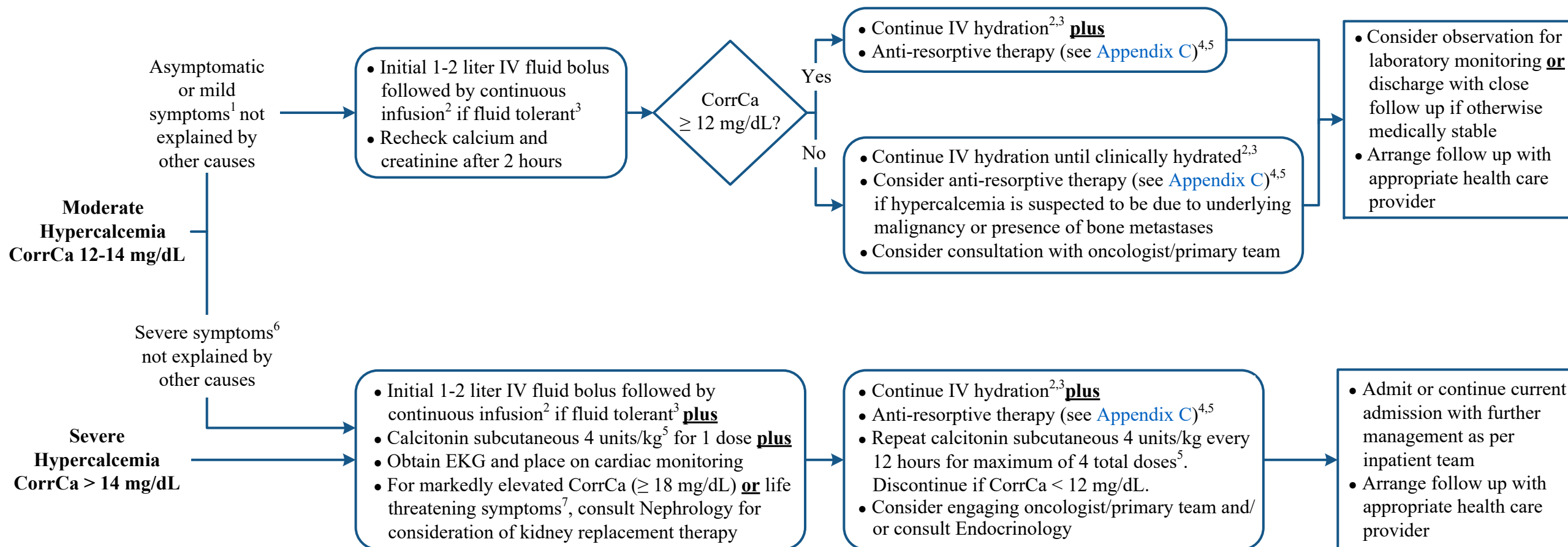
Acute Hospital Management of Hypercalcemia

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PRESENTATION/INITIAL TREATMENT

FOLLOW-UP/FURTHER TREATMENT

DISPOSITION



¹ Mild symptoms include constipation, confusion, nausea, abdominal pain, acute kidney injury (increase in creatinine of ≥ 0.3 mg/dL), fatigue, polyuria, and polydipsia

² Initial 1-2 liter IV bolus followed by continuous infusion of 100-200 mL/hour until clinically hydrated based on physical assessment and available lab values. Non-calcium containing IV fluids are recommended (e.g., isotonic saline solutions, Plasma-Lyte).

³ IV fluids should be used judiciously in patients predisposed to fluid overload (e.g., heart failure, advanced chronic kidney disease, ascites, anuric acute kidney injury, etc.) and should be guided by physical exam, laboratory findings, and imaging. Consider loop diuretics as needed to maintain fluid balance.

⁴ Risk of renal toxicity may be higher with bisphosphonates in the setting of dehydration. Adequate hydration is recommended prior to drug administration.

⁵ See [Appendix D](#) for drug information and formulary restrictions, dosing considerations, contraindications and adjunctive therapies

⁶ Severe symptoms include severe altered mental status, obtundation, stupor, coma, lethargy, obstipation, intractable nausea/vomiting, seizures, and EKG changes

⁷ Patients with life threatening symptoms may include those with or at risk for seizures, arrhythmias (including heart blocks, etc.), or obtundation/coma

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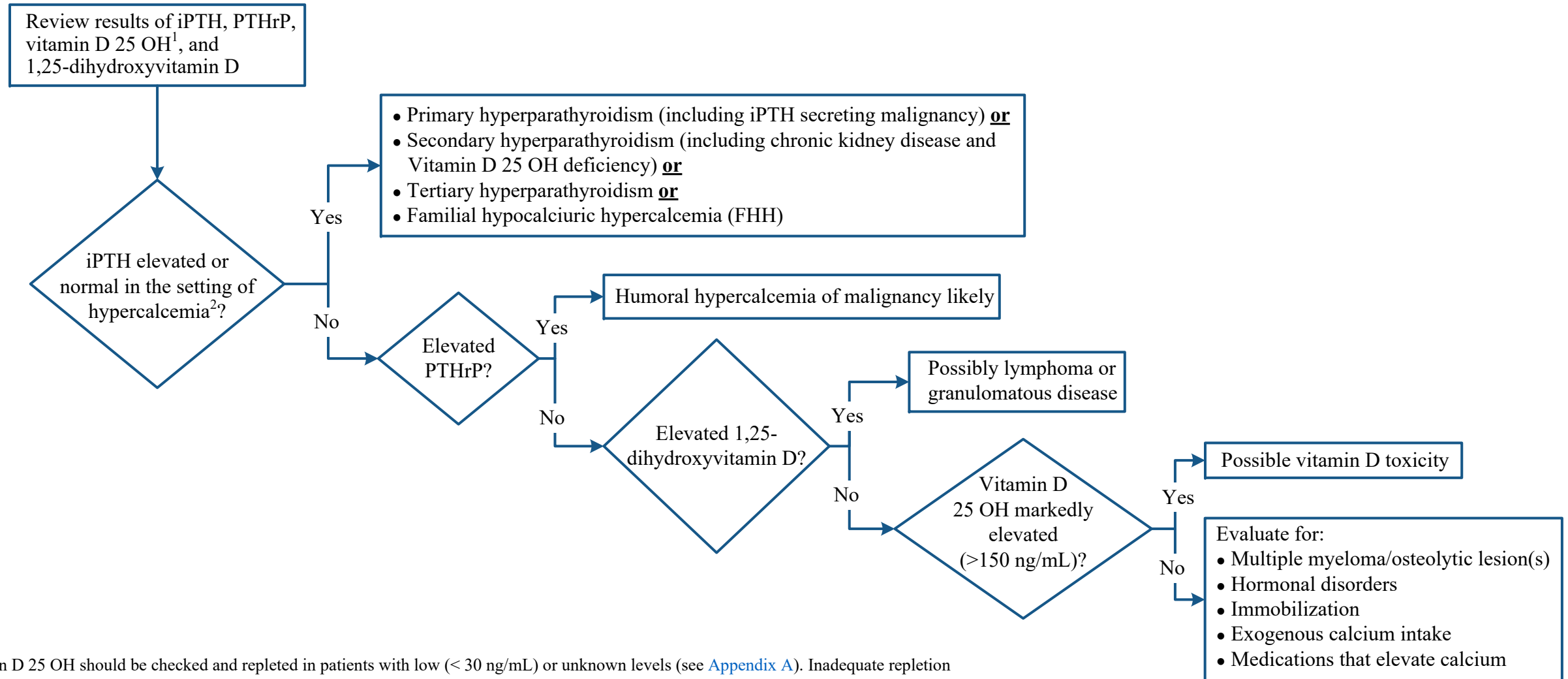
APPENDIX A: Vitamin D Repletion Recommendations

Vitamin D 25 OH Level	Repletion Recommendation
	<i>Repletion should ideally be initiated before or in conjunction with administration of an anti-resorptive agent. However, if this is not possible, repleting Vitamin D should NOT delay treatment of hypercalcemia.</i>
< 21 ng/mL	Administer ergocalciferol 50,000 units daily for three days, followed by 50,000 weekly for up to 8 weeks
21-29 ng/mL	- Administer ergocalciferol 50,000 units weekly for up to 8 weeks or - Administer cholecalciferol 1,000-2,000 units daily
≥ 30 ng/mL	Consider maintenance dosing of cholecalciferol 1,000-2,000 units daily if unable to maintain adequate dietary intake

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APPENDIX B: New Diagnosis Workup

- Note:**
- Regardless of etiology, initiate acute management for hypercalcemia as indicated on [Page 1](#)
 - Consider consult to Endocrinology for etiologies unrelated to hypercalcemia of malignancy



¹ Vitamin D 25 OH should be checked and repleted in patients with low (< 30 ng/mL) or unknown levels (see [Appendix A](#)). Inadequate repletion can lead to refractory hypocalcemia with bisphosphonate or denosumab use. Repleting Vitamin D should NOT delay treatment of hypercalcemia.

² PTH within the normal range with an elevated corrected calcium (≥ 10.3 mg/dL)

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APPENDIX C: Anti-resorptive Therapy Recommendations

Note: Treatment recommendations may not apply to patients on renal replacement therapy

Anti-resorptive Therapy History	Treatment Recommendations ¹
Anti-resorptive naïve	• Creatinine clearance (CrCl) ≥ 30 mL/minute: Administer zoledronic acid² 4 mg IV once over 15-60 minutes • CrCl < 30 mL/minute: Administer one of the following as clinically indicated (options listed alphabetically): ◦ Denosumab 120 mg subcutaneous once if inpatient formulary restriction criteria has been met¹ or ◦ Pamidronate² 60-90 mg IV once over 2-6 hours or ◦ Zoledronic acid² 4 mg IV once over 60 minutes
Received bisphosphonate or denosumab < 7 days ago	• Do NOT administer additional bisphosphonate or denosumab Note: The maximum calcium lowering effect for bisphosphonates is estimated to be ≤ 7 days. The maximal calcium lowering effect for denosumab is seen at 14-23 days. • Utilize supportive care measures to manage hypercalcemia including fluids and/or calcitonin if severe symptoms³ while awaiting onset of action of antiresorptive agent
Received bisphosphonate ≥ 7 days ago	• Administer denosumab 120 mg subcutaneous once (<i>preferred</i>) for treatment of hypercalcemia refractory to bisphosphonates or • Repeat dose of bisphosphonate² ◦ CrCl ≥ 30 mL/minute: Administer zoledronic acid 4 mg IV once over 15-60 minutes ◦ CrCl < 30 mL/minute: Administer one of the following as clinically indicated (options listed alphabetically): - Pamidronate² 60-90 mg IV once over 2-6 hours or - Zoledronic acid² 4 mg IV once over 60 minutes
Received denosumab ≥ 7 days ago	Repeat denosumab if clinically indicated. See Appendix D for recommended repeat dosing schedule. Note: The maximal calcium lowering effect for denosumab is seen at 14-23 days

¹ See [Appendix D](#) for drug information and formulary restrictions, dosing considerations, contraindications and adjunctive therapies

² Risk of renal toxicity may be higher with bisphosphonates in the setting of dehydration. Adequate hydration is recommended prior to drug administration.

³ Severe symptoms include severe altered mental status, obtundation, stupor, coma, lethargy, obstipation, intractable nausea/vomiting, seizures, and EKG changes

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APPENDIX D: Pharmacotherapy for Acute Hypercalcemia Treatment: Dosing and Considerations

Formulary Agents	Dosing	Considerations	Adverse Effects	Onset	Median Duration of Action
Calcitonin	• 4 units/kg subcutaneous every 12 hours • May increase to 8 units/kg if inadequate response	• Reserved for severe symptoms and/or severe hypercalcemia • Injection formulation only, intranasal is ineffective for acute treatment • Consider rounding to nearest 400 unit vial size • Limit duration to 48 hours due to tachyphylaxis	• Injection site reactions • Anaphylaxis	2-4 hours	6-8 hours
Denosumab	120 mg subcutaneous once	• Inpatient formulary restriction: Currently approved for ◦ Giant cell tumor of the bone or ◦ Hypercalcemia of malignancy with one or more of the following: - Refractory to bisphosphonate therapy - Severe renal impairment with eGFR < 30 mL/minute¹, acute kidney injury (AKI)², or receiving renal replacement therapy - History of or current renal deterioration due to bisphosphonate administration (creatinine > 50% from baseline) • Avoid in those with a history of osteonecrosis unless benefit outweighs risk. Consider dental oncology evaluation in patients with poor dentition. • Most potent antiresorptive agent • May cause severe hypocalcemia with increased risk in patients with renal dysfunction. Recommended to closely monitor within 14 days of injection. • May repeat on Day 8, 15, and 29. Then may be repeated every 4 weeks based on hypercalcemia status.	• Hypocalcemia³ • Hypophosphatemia • Osteonecrosis of the jaw	3-10 days (Time to complete response: 23 days)	104 days

¹ Eligibility is based on current guidance for renal function assessment using eGFR; however, drug dosing/dose adjustments should be determined according to drug information resources which may use creatinine clearance

² AKI defined as increase in creatinine by ≥ 0.3 mg/dL within 48 hours or increase in creatinine to ≥ 1.5 times of baseline

³ Vitamin D 25 OH should be checked and repleted in patients with low (< 30 ng/mL) or unknown levels (see [Appendix A](#)). Inadequate repletion can lead to refractory hypocalcemia with bisphosphonate or denosumab use. Repleting Vitamin D should NOT delay treatment of hypercalcemia.

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APPENDIX D: Pharmacotherapy for Acute Hypercalcemia Treatment: Dosing and Considerations - continued

Formulary Agents	Dosing	Considerations	Adverse Effects	Onset	Median Duration of Action
Fluids	Initial 1-2 liter IV bolus followed by continuous infusion of 100-200 mL/hour until clinically hydrated based on physical assessment and available lab values	- Non-calcium containing intravenous fluids are recommended (e.g., isotonic saline solutions, Plasma-Lyte) - IV fluids should be used judiciously in patients predisposed to fluid overload (e.g., heart failure, advanced chronic kidney disease, ascites, anuric acute kidney injury, etc.) and should be guided by physical exam, laboratory findings, and imaging. Consider loop diuretics as needed to maintain fluid balance.	- Fluid overload - Heart failure exacerbation	Minutes to hours	During infusion
Pamidronate	60-90 mg IV once over 2-6 hours - Contraindicated if creatinine > 4.5 mg/dL	- Risk of renal toxicity may be higher with bisphosphonates in the setting of dehydration. Adequate hydration is recommended prior to drug administration. - Avoid in those with a history of osteonecrosis unless benefit outweighs risk. Consider dental oncology evaluation in patients with poor dentition. - Less potent/effective than zoledronic acid and denosumab - May be repeated in 7 days if hypercalcemia persists	- Acute phase reaction with fever and myalgias up to 72 hours after infusion - Osteonecrosis of the jaw - Hypophosphatemia - Hypocalcemia¹ - Nephrotoxicity	48-72 hours (Time to complete response: 7 days)	7-14 days
Zoledronic Acid	4 mg IV once over 15-60 minutes - No dosage adjustment necessary for renal impairment when treating hypercalcemia - Consider increasing infusion time to 60 minutes for CrCl < 30 mL/minute - Contraindicated if creatinine > 4.5 mg/dL	- Risk of renal toxicity may be higher with bisphosphonates in the setting of dehydration. Adequate hydration is recommended prior to drug administration. - Avoid in those with a history of osteonecrosis unless benefit outweighs risk. Consider Dental Oncology evaluation in patients with poor dentition. - May be repeated in 7 days if hypercalcemia persists	- Acute phase reaction with fever and myalgias up to 72 hours after infusion - Osteonecrosis of the jaw - Hypophosphatemia - Hypocalcemia¹ - Nephrotoxicity	48-72 hours (Time to complete response: 7 days)	4-6 weeks

¹ Vitamin D 25 OH should be checked and repleted in patients with low (< 30 ng/mL) or unknown levels (see [Appendix A](#)). Inadequate repletion can lead to refractory hypocalcemia with bisphosphonate or denosumab use.

Repleting Vitamin D should NOT delay treatment of hypercalcemia.

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SUGGESTED READINGS

- Berenson, J. R., Rosen, L., Vescio, R., Lau, H. S., Woo, M., Sioufi, A., ... Seaman, J. J. (2013). Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *The Journal of Clinical Pharmacology*, 37(4), 285-290. doi:10.1002/j.1552-4604.1997.tb04304.x
- Chakhtoura, M., & Fuleihan, E. H. G. (2021). Treatment of Hypercalcemia of Malignancy. *Endocrinology and Metabolism Clinics*, 50(4), 781-792. doi:10.1016/j.ecl.2021.08.002
- Fuleihan, G. E., Clines, G. A., Hu, M. I., Marcocci, C., Murad, M. H., Piggott, T., ... Drake, M. T. (2023). Treatment of hypercalcemia of malignancy in adults: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, 108(3), 507-528. doi:10.1210/clinem/dgac621
- Guise, T. A., & Wysolmerski, J. J. (2022). Cancer-associated hypercalcemia. *New England Journal of Medicine*, 386(15), 1443-1451. doi:10.1056/NEJMcp2113128
- Hirschberg, R. (2012). Renal complications from bisphosphonate treatment. *Current Opinion in Supportive and Palliative Care* 6(3), 342-347. doi:10.1097/SPC.0b013e328356062e
- Hu, M. I. (2021). Hypercalcemia of Malignancy. *Endocrinology and Metabolism Clinics*, 50(4), 721-728. doi:10.1016/j.ecl.2021.07.003
- Hu, M. I., Glezerman, I. G., Leboulleux, S., Insogna, K., Gucalp, R., Misorowski, W., ... Jain, R. K. (2014). Denosumab for treatment of hypercalcemia of malignancy. *The Journal of Clinical Endocrinology and Metabolism*, 99(9), 3144-3152. doi:10.1210/jc.2014-1001
- Mirrakhimov, A. E. (2015). Hypercalcemia of malignancy: An update on pathogenesis and management. *North American Journal of Medical Sciences*, 7(11), 483. doi:10.4103/1947-2714.170600
- Reagan, P., Pani, A., & Rosner, M. H. (2014). Approach to diagnosis and treatment of hypercalcemia in a patient with malignancy. *American Journal of Kidney Diseases*, 63(1), 141-147. doi:10.1053/j.ajkd.2013.06.025
- Rosner, M. H., & Dalkin, A. C. (2012). Onco-nephrology: The pathophysiology and treatment of malignancy-associated hypercalcemia. *Clinical Journal of the American Society of Nephrology*, 7(10), 1722-1729. doi:10.2215/CJN.02470312
- Stewart, A. F. (2005). Hypercalcemia Associated with Cancer. *New England Journal of Medicine*, 352(4), 373-379. doi:10.1056/NEJMcp042806
- Tanvetyanon, T., & Stiff, P. J. (2006). Management of the adverse effects associated with intravenous bisphosphonates. *Annals of Oncology*, 17, 897-907. doi:10.1093/annonc/mdj105
- Terpos E., Christoulas D., & Gavriatopoulou, M. (2018). Biology and treatment of myeloma related bone disease. *Metabolism*, 80, 80-90. doi:10.1016/j.metabol.2017.11.012
- Thosani, S., & Hu, M. I. (2015). Denosumab: A new agent in the management of hypercalcemia of malignancy. *Future Oncology*, 11(21), 2865-2871. doi:10.2217/fon.15.232
- Walker, M. D., & Shane, E. (2022). Hypercalcemia: A Review. *Journal of the American Medical Association*, 328(16), 1624-1636. doi:10.1001/jama.2022.18331

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DEVELOPMENT CREDITS

This practice consensus statement is based on majority opinion of the Hypercalcemia workgroup at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

Core Development Team Leads

Sonya Khan, MD (Endocrine Neoplasia and HD)
Adriana Wechsler, MD (Emergency Medicine)

Workgroup Members

Melody Becnel, MD (Lymphoma-Myeloma)
Norman Brito-Dellan, MD (Hospital Medicine)
Henry Cao, PharmD (Pharmacy Clinical Programs)
Aysha Chaudhri, MD (Endocrine Neoplasia and HD)
Ashley Crouch, PharmD (Pharmacy Clinical Programs)
Olga N. Fleckenstein, BS♦
Amit Lahoti, MD (Nephrology)
Maggie Ma, PharmD (Pharmacy Clinical Programs)
Alyssa Mohammed, MD (Hospital Medicine)

Arlene Siefker-Radtke, MD (Genitourinary Medical Oncology)
Princey Thomas, APRN (Hospital Medicine)
Sonali Thosani, MD (Endocrine Neoplasia and HD)
William Towers, PharmD (Pharmacy Clinical Programs)
Jeena Varghese, MD (Endocrine Neoplasia and HD)
Mohammad Waleed, PharmD (Pharmacy Clinical Programs)
Mary Lou Warren, DNP, APRN, CNS-CC♦
Caroline Wesonga, APRN (Hospital Medicine)

♦ Clinical Effectiveness Development Team