Acute Hospital Management of Hypercalcemia[1]

PRESENTATION/INITIAL EVALUATION

Patient presenting with laboratory evidence or signs/symptoms of hypercalcemia[2,3]

- History and physical exam:
  - History of recurrent/refractory hypercalcemia **or** prior treatment with anti-resorptive agents
  - History of chronic kidney disease (CKD)
  - Assess patient volume status
  - Dental history and history of osteonecrosis of the jaw[4]
  - Identify and consider discontinuing medications that may contribute to hypercalcemia (*e.g.,* calcium supplements, vitamin D, thiazide diuretics, lithium)
  - Cancer history and/or imaging confirming bone metastasis
  - Consider non-malignant reasons[5]
- Labs:
  - Calcium[6], creatinine, albumin, phosphorous, and vitamin D 25 OH[7]
  - If new diagnosis or clinically indicated, parathyroid hormone (iPTH), parathyroid hormone-related peptide (PTHrP), 1,25-dihydroxyvitamin D, thyroid stimulating hormone (TSH) and free T4 (see Appendix B: New Diagnosis Workup)
  - Consider C-telopeptide (CTX)[8]
- Calculate Corrected Calcium: [(4 – albumin) x 0.8] + calcium

FINDINGS

Mild Hypercalcemia Corrected Calcium (CorrCa) 10.3-11.9 mg/dL

Symptomatic[2,3]?

TREATMENT

Yes → Treat as Moderate Hypercalcemia; see Page 2

No → Initial 1-2 liter IV fluid bolus followed by continuous infusion[9] if fluid tolerant[10]

- Continue IV hydration until clinically hydrated[9,10]
- Consider anti-resorptive therapy (see Appendix C)[11,12] if hypercalcemia is suspected to be due to underlying malignancy or presence of bone metastases
- Consider consultation with oncologist/ primary team

DISPOSITION

- Consider discharge if otherwise medically stable
- Arrange follow up with appropriate health care provider

Moderate Hypercalcemia CorrCa 12-14 mg/dL → See Page 2

Severe Hypercalcemia CorrCa >14 mg/dL → See Page 2

[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 (CO_2) 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

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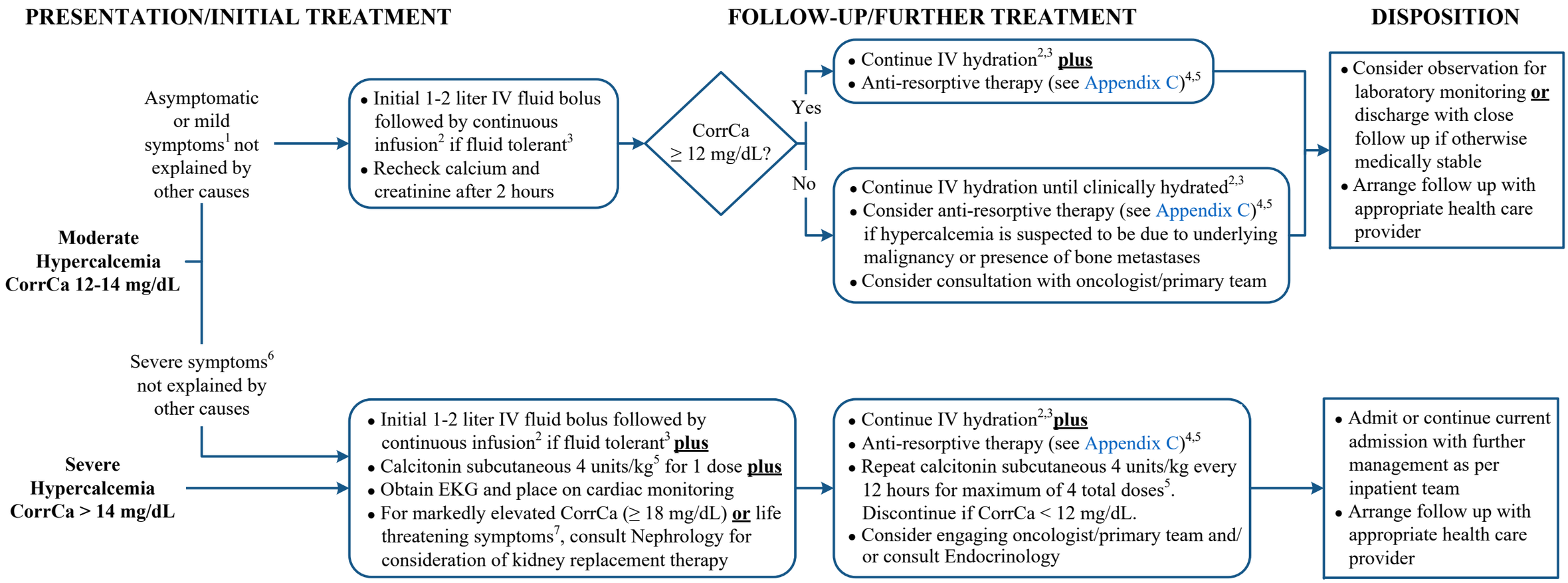
Acute Hospital Management of Hypercalcemia

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] 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, arrythmias (including heart blocks, *etc*.), or obtundation/coma

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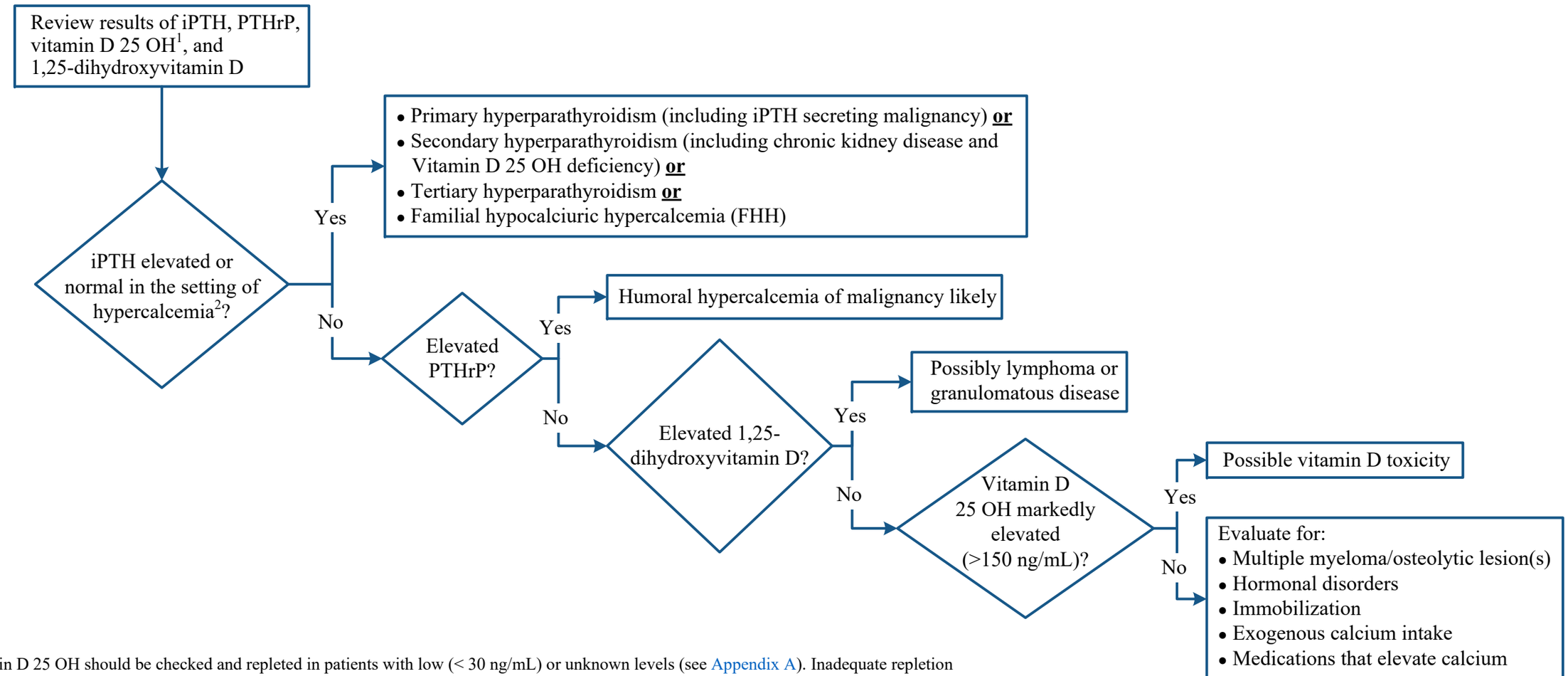
APPENDIX A: Vitamin D Repletion Recommendations

Vitamin D 25 OH Level	**Repletion Recommendation** *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.*
< 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

Acute Hospital Management of Hypercalcemia

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 acid[2] 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 met[1] **or** ◦ Pamidronate[2] 60-90 mg IV once over 2-6 hours **or** ◦ Zoledronic acid[2] 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 symptoms[3] while awaiting onset of action of antiresorptive agent
Received bisphosphonate ≥ 7 days ago	• Administer denosumab 120 mg subcutaneous once *(preferred)* for treatment of hypercalcemia refractory to bisphosphonates **or** • Repeat dose of bisphosphonate[2] ◦ 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): - Pamidronate[2] 60-90 mg IV once over 2-6 hours **or** - Zoledronic acid[2] 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

Acute Hospital Management of Hypercalcemia

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/minute[1], 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.	• Hypocalcemia[3] • 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.

Continued on next page

Acute Hospital Management of Hypercalcemia

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 • Hypocalcemia[1] • 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 • Hypocalcemia[1] • 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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