Chapter 27
Approach to Hypercalcemia in the ICU

27.1 Introduction

Hypercalcemia, defined as an abnormally elevated level of calcium in the blood, is a common electrolyte disorder with significant clinical consequences. Calcium plays a crucial role in various physiological processes, including neuromuscular function, blood coagulation, and bone metabolism. In the bloodstream, calcium exists in three distinct fractions: ionized calcium (approximately 50%), which is the biologically active form; protein-bound calcium, primarily attached to albumin (about 40%); and calcium complexed with anions like phosphate and citrate (around 10%). The management of hypercalcemia, especially in the intensive care unit (ICU), is critical because severe cases can lead to life-threatening complications such as cardiac arrhythmias, renal failure, and neurological impairments [1].

Calcium homeostasis is tightly regulated by a complex interplay of hormones, notably parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25(OH)_2D], and fibroblast growth factor 23 (FGF-23). Disruptions in this regulatory system can result from various conditions, including malignancies, primary hyperparathyroidism, granulomatous diseases, thyrotoxicosis, and prolonged immobilization. Effective management involves assessing the severity of hypercalcemia, identifying the underlying cause, and implementing appropriate treatment strategies to normalize calcium levels and prevent complications [2] [Ref: Algorithm 27.1].

27.2 Pathophysiology of Calcium Regulation

Understanding calcium regulation is essential for diagnosing and managing hypercalcemia. Calcium homeostasis is maintained through a balance of intestinal absorption, renal excretion, and bone remodeling. Key hormones involved include:

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- Parathyroid Hormone (PTH): Secreted by the parathyroid glands in response to low serum calcium levels, PTH increases calcium levels by stimulating osteoclast-mediated bone resorption, enhancing renal reabsorption of calcium, and promoting the activation of vitamin D to its active form.
- 1,25-Dihydroxyvitamin D [1,25(OH)_2D]: The active form of vitamin D enhances intestinal absorption of calcium and phosphate and works synergistically with PTH to regulate bone remodeling.
- Fibroblast Growth Factor 23 (FGF-23): Produced by osteocytes and osteoblasts, FGF-23 regulates phosphate metabolism and indirectly influences calcium levels by modulating vitamin D activity.

27.3 Ionized Calcium vs. Total Calcium

In clinical practice, measuring ionized calcium is preferable when available, as it reflects the biologically active fraction responsible for physiological effects. Total serum calcium measurements can be misleading, especially in patients with abnormal serum albumin levels or acid-base disturbances, as they do not accurately represent the ionized fraction. Although corrected calcium calculations attempt to adjust for albumin levels, they may not always be precise, particularly in critically ill patients. Therefore, relying on ionized calcium provides a more accurate assessment for diagnosis and treatment.

27.4 Clinical Manifestations

The symptoms of hypercalcemia correlate with both the absolute level of serum calcium and the rate at which it rises:

Mild Hypercalcemia (≤11.5 mg/dL):

- Often asymptomatic.
- May present with vague neuropsychiatric symptoms such as fatigue, depression, or mild cognitive impairment.

Moderate Hypercalcemia (11.5–14 mg/dL):

- Gastrointestinal Disturbances: Nausea, vomiting, constipation, and anorexia.
- Renal Impairment: Polyuria, polydipsia, and dehydration due to nephrogenic diabetes insipidus.
- Neuropsychiatric Symptoms: Confusion, irritability, or depression.
- Cardiovascular Effects: Hypertension and shortened QT interval.

Severe Hypercalcemia (>14 mg/dL):

- Neurological symptoms can progress from lethargy and stupor to coma.

- Severe gastrointestinal symptoms, including vomiting and pancreatitis.
- Cardiovascular Complications: Arrhythmias and possible cardiac arrest.
- Peptic ulcer disease due to increased gastrin secretion.

27.5 Causes of Hypercalcemia

Hypercalcemia arises from increased calcium entry into the circulation, decreased renal excretion, or a combination of both. The causes can be broadly categorized into PTH-dependent and PTH-independent mechanisms.

1. **PTH-Dependent Hypercalcemia:**
   Primary Hyperparathyroidism:

   - Most common cause in outpatients.
   - Usually due to a parathyroid adenoma leading to excessive PTH secretion.
   - Results in increased bone resorption, renal calcium reabsorption, and intestinal calcium absorption.

   Tertiary Hyperparathyroidism:

   - Occurs in patients with chronic renal insufficiency.
   - Prolonged secondary hyperparathyroidism leads to autonomous PTH secretion and hypercalcemia.

   Familial Hypocalciuric Hypercalcemia (FHH):

   - Genetic condition caused by mutations in the calcium-sensing receptor.
   - Characterized by mild hypercalcemia, low urinary calcium excretion, and inappropriately normal or slightly elevated PTH levels.

2. **PTH-Independent Hypercalcemia:**
   Malignancy-Associated Hypercalcemia:

   - Humoral Hypercalcemia of Malignancy (HHM):
   - Caused by secretion of PTH-related protein (PTHrP) by tumors such as squamous cell carcinomas, renal cell carcinoma, and breast cancer.
   - PTHrP mimics the effects of PTH, leading to increased bone resorption and renal calcium reabsorption.

   Local Osteolytic Hypercalcemia:

   - Seen in cancers with bone metastases, such as breast cancer and multiple myeloma.
   - Tumor cells produce cytokines that stimulate osteoclasts, leading to bone resorption and calcium release.

Granulomatous Diseases:

- Diseases like sarcoidosis and tuberculosis involve activated macrophages that increase extrarenal production of 1,25(OH)_2D.
- Leads to enhanced intestinal calcium absorption independent of PTH.

Thyrotoxicosis:

- Excess thyroid hormones stimulate bone turnover, increasing bone resorption and serum calcium levels.

Immobilization:

- Prolonged immobilization, particularly in individuals with high bone turnover (e.g., adolescents, Paget's disease), leads to increased osteoclastic activity and bone resorption.

Vitamin D Intoxication:

- Excessive intake of vitamin D supplements or overproduction due to granulomatous disease increases intestinal absorption of calcium.

Medications:

- Thiazide Diuretics: Reduce renal calcium excretion.
- Lithium: Increases PTH secretion.
- Vitamin A Excess: Stimulates osteoclast activity.

Milk-Alkali Syndrome:

- Results from excessive intake of calcium and absorbable alkali.
- Leads to hypercalcemia, metabolic alkalosis, and renal impairment.

Adrenal Insufficiency:

- May cause mild hypercalcemia due to hemoconcentration and increased bone resorption.

27.6 Diagnostic Approach

The evaluation of hypercalcemia involves confirming elevated calcium levels and determining the underlying cause.

1. **Confirm Hypercalcemia:**

- Measure Ionized Calcium:
- Preferred method as it reflects the biologically active fraction.
- Avoids inaccuracies due to variations in albumin or pH levels.
- Correct Total Calcium:
- If ionized calcium is unavailable, adjust total calcium for serum albumin:

$$\text{Corrected Calcium}\left(\text{mg/dL}\right) = \text{Measured Total Calcium} + \left[0.8 \times \left(4.0 - \text{Serum Albumin}\left(\text{g/dL}\right)\right)\right]$$

2. **Assess Parathyroid Hormone (PTH) Levels:**
   - Elevated or Inappropriately Normal PTH:
   - Suggests PTH-dependent causes like primary hyperparathyroidism or FHH.
   - Suppressed PTH:
   - Indicates PTH-independent hypercalcemia.
   - Prompts evaluation for malignancy, vitamin D intoxication, granulomatous disease, or other causes.
3. **Additional Investigations:**
   PTHrP Levels:
   - Elevated in humoral hypercalcemia of malignancy.
   - Order when malignancy is suspected.

   Vitamin D Metabolites:
   - 25(OH)D: Elevated in vitamin D intoxication.
   - 1,25(OH)_2D: Elevated in granulomatous diseases and some lymphomas.

   Thyroid Function Tests:
   - To assess for thyrotoxicosis.

   Bone Imaging:
   - If local osteolytic hypercalcemia is suspected.

   Urinary Calcium Excretion:
   - Low in FHH.
   - High in primary hyperparathyroidism.

27.7 Management by Severity

27.7.1 Mild Hypercalcemia

- Observation and Investigation:
- Focus on identifying and treating the underlying cause.
- Ensure adequate hydration.
- Avoid factors that can worsen hypercalcemia, such as thiazide diuretics and high calcium intake.

27.7.2 Moderate to Severe Hypercalcemia

Management aims to reduce serum calcium levels rapidly and address the underlying cause.

1. **Hydration and Renal Calcium Excretion:**

- Intravenous Normal Saline:
- Administer aggressively (e.g., 200–300 mL/h) to correct volume depletion.
- Enhances glomerular filtration rate and promotes calciuresis.
- Loop Diuretics:
- Furosemide:
- Used after rehydration to promote diuresis and calciuresis.
- Monitor electrolytes to prevent hypokalemia and hypomagnesemia.

2. **Inhibition of Bone Resorption:**

- Bisphosphonates:
- Zoledronic Acid: 4 mg IV over 15 min.
- Pamidronate: 60–90 mg IV over 2–4 h.
- Inhibit osteoclast-mediated bone resorption.
- Onset of action is 48–72 h.
- Denosumab:
- Monoclonal antibody against RANKL.
- Effective in patients resistant or intolerant to bisphosphonates.
- Particularly useful in malignancy-associated hypercalcemia.

3. **Calcitonin:**

- Mechanism:
- Rapidly reduces serum calcium by inhibiting osteoclast activity and increasing renal calcium excretion.
- Administration:
- Given subcutaneously or intramuscularly.
- Tachyphylaxis develops within 48 h, limiting long-term use.

4. **Glucocorticoids:**

- Indications:
- Hypercalcemia due to vitamin D intoxication or granulomatous diseases.
- Reduce intestinal calcium absorption and inhibit 1,25(OH)_2D production.
- Dosage:
- Prednisone 40–60 mg daily.

5. **Dialysis:**

- Indications:
- Severe, life-threatening hypercalcemia refractory to medical therapy.
- Patients with renal failure or contraindications to aggressive hydration.
- Procedure:
- Hemodialysis with low-calcium dialysate.

27.8 Prognosis and Complications

Malignancy-Associated Hypercalcemia:

- Carries a poor prognosis.
- Median survival ranges from 25 to 52 days in severe cases.
- Hypercalcemia often indicates advanced disease [3].

Renal Complications:

- Nephrocalcinosis and renal insufficiency due to prolonged hypercalcemia.
- Cardiovascular Effects:
- Risk of arrhythmias and hypertension due to shortened QT interval.

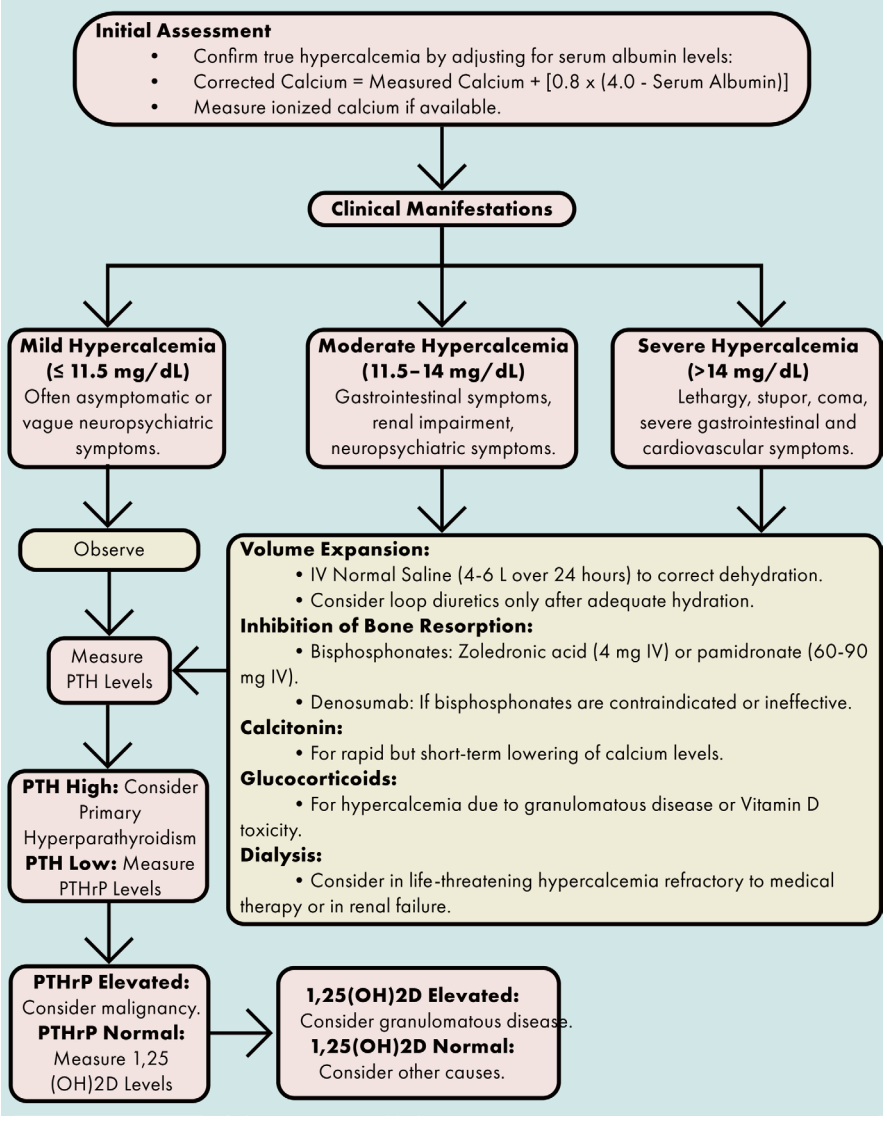
Neurological Effects:

- Cognitive dysfunction, neuromuscular weakness, and, in severe cases, coma.

27.9 Conclusion

Effective management of hypercalcemia requires a comprehensive understanding of calcium homeostasis and a methodical diagnostic approach to identify the underlying cause. Early recognition and prompt treatment are vital, particularly in severe cases, to prevent life-threatening complications. Clinicians should focus on stabilizing the patient through hydration and medications that reduce serum calcium levels while addressing the primary etiology to prevent recurrence.

Algorithm 27.1: Approach to hypercalcemia in the ICU



Bibliography

1. Murray SL, Wolf M. Calcium and phosphate disorders: core curriculum 2024. Am J Kidney Dis. 2024;83(2):241–56.
2. Bushinsky DA, Monk RD. Electrolyte quintet: calcium. Lancet. 1998;352(9124):306–11.
3. Guise TA, Wysolmerski JJ. Cancer-associated hypercalcemia. N Engl J Med. 2022;386(15):1443–51.