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Research Article

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Hypercalcemia in the Emergency Department: Evidence-Based Diagnosis and Acute Management

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Abstract

Introduction: *Hypercalcemia is a life-threatening electrolyte imbalance that frequently presents to the Emergency Department (ED). Approximately 90% of cases are attributed to primary hyperparathyroidism and malignancy.*

Purpose: *The aim of this updated review is to summarize diagnostic and therapeutic management strategies based on current international guidelines.*

Method: *Narrative synthesis of literature published between 2010–2025, with a clinical focus on ED management.*

Results: *The diagnosis should be confirmed with ionized calcium assessment, disease severity categorization, and electrocardiography (ECG). Acute management comprises isotonic saline hydration, calcitonin bridging, and definitive antiresorptive (zoledronic acid or denosumab). In calcitriol-mediated disease, glucocorticoids are the therapy of choice; dialysis is indicated if refractory or severe. Guided goal-directed fluid therapy with point-of-care ultrasound (POCUS) minimizes iatrogenic injury.*

Conclusion: *A stepwise, risk-stratified ED algorithm that incorporates fluids, pharmacotherapy, POCUS-guided evaluation, and escalation criteria maximizes safety and outcomes in hypercalcemic emergencies.*

Keywords: Hypercalcemia, Emergency Medicine, Parathyroid Hormone, Malignancy, Bisphosphonates, Denosumab; Point-of-Care Ultrasound.

Introduction

Hypercalcemia, defined as a serum calcium level >2.60 mmol/L (>10.5 mg/dL), is a common metabolic emergency. While mild cases are often incidental, acute or severe hypercalcemia (>3.5 mmol/L; >14 mg/dL) may cause neuropsychiatric, renal, and cardiovascular complications. The overwhelming majority of cases are due to either primary hyperparathyroidism (PHPT) or malignancy-associated hypercalcemia (MAH). Emergency physicians must rapidly recognize and stabilize this condition, often in collaboration with endocrinology, nephrology, and oncology specialists [1-4].

Pathophysiology

The control of calcium homeostasis is a precisely regulated balance between parathyroid hormone (PTH), vitamin D metabolites, renal function, and bone metabolism. Hypercalcemia occurs when there is a deranged balance between intestinal calcium absorption, bone resorption, and renal calcium excretion.

The most frequent cause of PTH-mediated hypercalcemia is primary hyperparathyroidism (PHPT) through over-secretion of PTH leading to osteoclastic bone resorption and inhibition of Ca reabsorption in the renal tubules (with the parallel reduction of phosphate reabsorption). Habitually high PTH levels may stimulate calcitriol production as well that would promote intestinal calcium absorption. In tertiary hyperparathyroidism--frequently seen in the setting of chronic renal disease--autonomous parathyroid hyperplasia sustains hypercalcemia by a similar process.

Contrastingly, PTH-independent hypercalcemia is often related to cancer through various mechanisms. The most frequent pattern is by the secretion of PTHrP, which mimics the action of PTH on bone and kidney but does not respond to the regulatory feedback of intact PTH [5]. A second mechanism is osteolytic hypercalcemia, seen in multiple myeloma and bone metastasis, in which osteoclastic activity is stimulated by cytokines released by the tumor. One less common but clinically important etiology is ectopic calcitriol synthesis by, generally lymphoma cells or granulomatous tissue, resulting from increased intestinal calcium absorption.

In addition to this, several other causes are implicated in hypercalcemia. Extrarenal generation of calcitriol from 25-hydroxyvitamin D is enhanced by granulomatous diseases (sarcoidosis, tuberculosis). Vitamin D intoxication causes prolonged calcium reabsorption from the intestine. Drugs, such as thiazide diuretics, reducing renal calcium excretion and lithium, a drug that affects the PTH set point are established causes. Adrenal insufficiency and thyrotoxicosis could also have complex metabolic interactions, and both may be associated with hypercalcemia. When immobilized, there is rapid calcium efflux from bone, especially in young people with active bone turnover. Finally, milk-alkali syndrome, resulting from excessive calcium carbonate and absorbable alkali intake, has returned as an important etiology of hypercalcemia in the over-the-counter supplements era [6, 7].

Clinical Presentation

Hypercalcemia is clinically heterogeneous and not only depends on serum calcium level but also on the magnitude of the acute increase and the patient's pretreatment condition. Chronic, slowly increasing hypercalcemia (e.g., PHPT) may be well tolerated at higher calcium levels, and conversely, the patients with acute increases in serum calcium (e.g., malignancy-related hypercalcemia) often become symptomatic at quite modest concentrations. The traditional "stones, bones, abdominal groans, and psychiatric overtones" template is still somewhat helpful.

Kidney Stone Involvement

Polyuria and polydipsia are early signs occurring secondary to nephrogenic diabetes insipidus due to renal inability to concentrate urine. Long-standing hypercalcemia leads to nephrolithiasis and nephrocalcinosis, but acute increases cause acute kidney damage via vasoconstriction and intratubular calcium precipitation.

Bones

Skeletal symptoms— Patients may have described diffuse pain in the bones, fragility fractures, or osteitis fibrosa cystica in the setting of chronic PHPT. Cortical bone is lost due to the increase in osteoclastic activity, which particularly afflicts the load-bearing skeleton.

Gastrointestinal complaints ("Abdominal Groans")

Associated symptoms can include nausea, vomiting, anorexia, constipation, and abdominal pain. Lowered smooth muscle tonus and disturbed neural transmission leads to interference with peristalsis. Pancreatitis and peptic ulcer disease can develop in serious cases.

Neuropsychiatric ("Psychiatric Overtones")

can range from fatigue and irritability to depression and cognitive dysfunction and, in its most severe form, confusion, delirium, psychosis, seizures, and coma. The intensity of neurological impairment frequently seems to be related to the speed of the increase in calcium.

Cardiac

Hypercalcemia shortens the QT interval of the patient's ECG, increasing the risk for arrhythmias, and may induce hypertension due to an enhanced vascular tone. At extremely high levels (>3.5–4.0 mmol/L) patients are prone towards ventricular arrhythmias, heart block and cardiac arrest [8].

Variability in the clinical presentation emphasizes the need for integration of biochemical findings with clinical status. Mild neuropsychiatric or gastrointestinal presentations often preceded the catastrophic complications and emphasize the requirement to maintain a high level of suspicion in the ED.

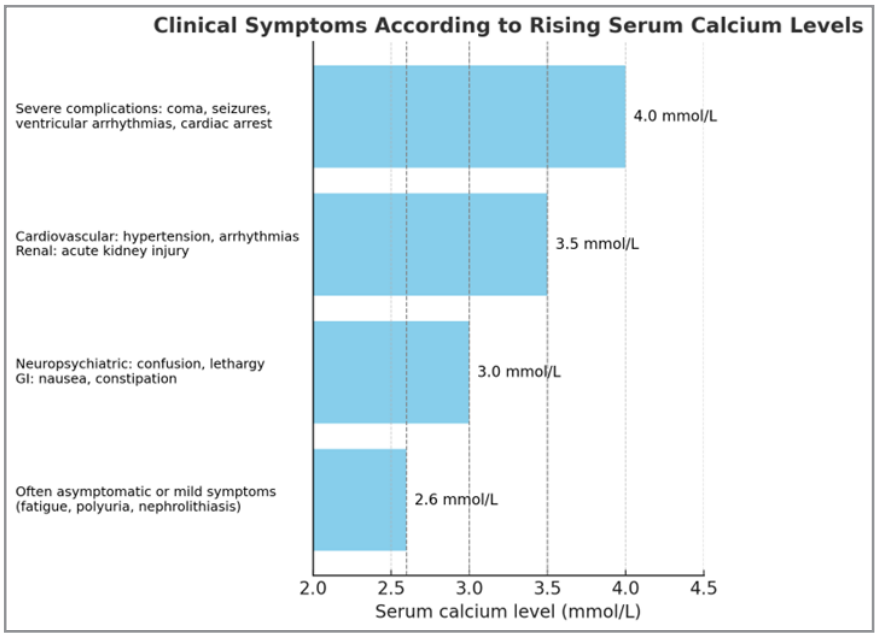

Figure 1: Clinical Symptoms Related to Calcium Levels

Emergency Medicine Diagnostic and Management Pathways
Diagnostic Evaluation

Diagnosis must be confirmed by measurement of ionized calcium, the physiologically active fraction. In settings where this is unavailable, corrected total calcium may be used, although this is less accurate in critical illness. Severity stratification is essential: mild 2.6–3.0 mmol/L, moderate 3.0–3.5 mmol/L, and severe >3.5 mmol/L. In The laboratory panel should include electrolytes, creatinine, phosphate, magnesium, venous/arterial blood gas, PTH, and 25-hydroxyvitamin D. In suspected malignancy, PTHrP should be measured; in granulomatous disease or lymphoma, 1,25-dihydroxyvitamin D is recommended. ECG is mandatory as hypercalcemia often produces QT shortening and can lead to arrhythmias. POCUS assessment of IVC diameter, collapsibility, lung B-lines, and Vexus grading provides dynamic fluid assessment, especially in elderly or renal/cardiac patients [9].

Emergency Management

First-line treatment is isotonic saline infusion at 200–300 mL/h, titrated according to urine output, hemodynamic status, and POCUS findings. Loop diuretics are indicated only after achieving euvolemia or in fluid overload. Calcitonin (4 IU/kg SC/IM every 12 h) has a rapid onset (4–6 h) but transient effect due to tachyphylaxis within 48 h. It serves as bridging therapy until definitive measures take effect.

Bisphosphonates are the gold standard for malignancy-related hypercalcemia. Zoledronic acid (4 mg IV) or pamidronate (60–90 mg IV) reduce osteoclastic activity, with onset in 48–72 h and prolonged efficacy lasting weeks [10].

Denosumab

(120 mg SC) is highly effective in patients with renal impairment or bisphosphonate-resistant hypercalcemia [11].

Glucocorticoids

(prednisone 40–60 mg/day) are indicated in calcitriol-mediated hypercalcemia, such as lymphoma or sarcoidosis [12]. Cinacalcet may be considered in PHPT crisis or parathyroid carcinoma when surgery is delayed.

Hemodialysis with a Low-calcium Bath

Is reserved for refractory or severe cases, especially in the context of renal failure or fluid intolerance [13].

Supplementary Table 1: ED Order Set – Hypercalcemia

Step	Orders / Actions	Notes
Triage	ECG, neuro check, ionized calcium	Red flags: altered mental status, arrhythmia
Labs	CBC, CMP, Mg, phosphate, PTH, vitamin D	Add PTHrP (if malignancy) or 1,25-OH2D (if lymphoma/granulomatous)
Stop meds	Thiazides, lithium, vitamin D, calcium supplements	Remove contributing factors
Fluids	0.9% NaCl 200–300 mL/h	Use POCUS (IVC, lung B-lines, VExUS) to titrate
Bridge	Calcitonin 4 IU/kg SC/IM q12h (≤48 h)	Rapid effect, tachyphylaxis ≤48 h
Definitive	Zoledronic acid IV or Denosumab SC	Early initiation in malignancy-related cases
Etiology-specific	Steroids (calcitriol-mediated); Cinacalcet (PHPT crisis)	Specialty input required
Escalation	Dialysis with low-Ca bath	For refractory/severe or renal failure
Monitoring	ECG, strict I&O, electrolytes q4–6h	Monitor for hypocalcemia after antiresorptives

Supplementary Table 2: POCUS-Guided Fluid Algorithm

Step	Ultrasound finding	Action
Baseline	IVC <1.5 cm, >50% collapsibility; lungs dry	Continue fluids
Reassess	IVC >2.0 cm, minimal collapse; B-lines >3	Reduce/stop fluids, consider diuretic
Advanced	VExUS grade 2–3 (severe venous congestion)	Avoid fluids, escalate to dialysis

Disposition

Patients with severe hypercalcemia, symptomatic moderate hypercalcemia, acute kidney injury, or those requiring antiresorptive therapy should be admitted to hospital wards. Intensive care unit admission is necessary in cases of coma, malignant arrhythmias, shock, or need for urgent dialysis.

Conclusion

Hypercalcemia represents a frequent and potentially fatal metabolic emergency in the ED. A systematic approach—including confirmation of ionized calcium, severity stratification, ECG and POCUS monitoring, evidence-based pharmacotherapy, and escalation to dialysis when indicated—forms the cornerstone of safe management. Standardized ED order sets and structured algorithms promote uniformity of care, enhance outcomes, and strengthen interdisciplinary collaboration.

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