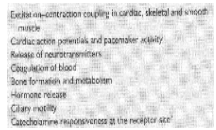
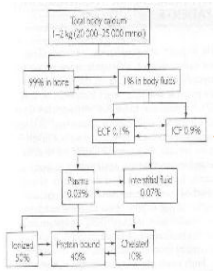
calcium disorders [created by Paul Young 18/12/07]

general

- Calcium is a highly regulated, ubiquitous cation that has multiple roles in the body.
- changes in intracellular calcium concentration affect a myriad of cell functions, including cell death or apoptosis; the duration and strength of cardiac muscle contraction; and smooth muscle contraction in blood vessels, airways, and the uterus



calcium homeostasis



		mg/day
Gastrointestinal tract	Diet	600–1200
	Absorbed	200–400
	Secreted	150–800
Renal	Filtered	11 000
	Reabsorbed (97% in the proximal convoluted tubule)	10 800
	Urinary calcium	200
Bone	Turnover	600–800

- Calcium exists in the extracellular plasma in a free ionized state as well as bound to other molecules.
- "Normal" plasma concentrations of total calcium vary between laboratories, but the range of (bound and unbound) calcium is 2.2 - 2.5 mmol/L). The biologically inert bound fraction (55% of the total) binds to proteins.
- Changes in albumin alter total calcium concentrations significantly, since the majority of protein-bound calcium associates with albumin.
- A small percentage of calcium is associated with other proteins, such as beta-globulins, or nonprotein molecules such as phosphate and citrate.
- Forty-five percent of the total calcium is biologically active and exists in the ionized form. Ionized calcium concentrations are inversely affected by the pH of blood; an increase in pH will decrease the ionized calcium concentration by 0.36 mmol/L, such that patients with metabolic alkalosis often are hypocalcemic.

some specific causes of hypercalcemia

Hyperparathyroidism
(i) primary hyperparathyroidism
- The most common cause of primary hyperparathyroidism is a parathyroid adenoma (85%).
- Parathyroid hyperplasia affects all glands and is the underlying cause of primary hyperparathyroidism in 10% of cases. It can be associated with the multiple endocrine neoplasia I and IIa syndromes. Multiple endocrine neoplasia I includes hyperparathyroidism, pituitary adenoma, and pancreatic tumors (most commonly insulinomas or gastrinomas). Multiple endocrine neoplasia IIa includes hyperparathyroidism, medullary carcinoma of the thyroid, and pheochromocytoma.
- Parathyroid carcinoma is a rare (<1% of cases) cause of primary hyperparathyroidism.
(ii) secondary hyperparathyroidism
- Secondary hyperparathyroidism results from stimuli outside the normal feedback loop. For example, patients with renal failure have decreased renal conversion of 25-hydroxyvitamin D to 1,25(OH)2D, resulting in less calcium absorption. In addition, these patients have hyperphosphatemia. The cumulative effect is that these patients are hypocalcemic, and PTH is secreted from the parathyroid glands.
(iii) tertiary hyperparathyroidism
- Tertiary hyperparathyroidism occurs when the parathyroid glands of these patients become overactive and autonomous from normal negative feedback mechanisms. Patients who fail medical therapy and acquire tertiary hyperparathyroidism develop clinical sequelae such as calciphylaxis, and they should be referred for parathyroidectomy.

Hypercalcemia of Malignancy.
- Hypercalcemia of malignancy is most commonly secondary to the inappropriate release of PTH-related peptide (PTHrp) from tumor cells. This leads to increased bone resorption and decreased renal calcium excretion.
- PTHrp induced hypercalcemia is associated with squamous cell (e.g., lung), breast, prostate, and (rarely) colon cancer as well as adult T-cell malignancies and multiple myeloma

Granulomatous Diseases.
- The association between hypercalcemia and granulomatous diseases such as sarcoidosis occurs secondary to increased 1,25(OH)2D production that is independent from the normal negative feedback mechanisms.
- Macrophages in granulomas produce 1,25(OH)2D.
- Other granulomatous disease such as tuberculosis, leprosy, coccidioidomycosis, and histoplasmosis all have been associated with hypercalcemia via a similar pathway.

Diet and Drugs.
- Patients with elevated calcium concentrations should be screened to exclude dietary causes. Large amounts of supplemental calcium or vitamin D (e.g., in the form of antacids) can cause hypercalcemia.

symptoms of hypercalcaemia

- Gastrointestinal symptoms result from smooth muscle relaxation and include constipation, anorexia, nausea, and vomiting.
- Neurologically, patients with hypercalcemia can be lethargic, hypotonic,confused, or even comatose.
- Effects on the kidneys include polyuria, dehydration, and nephrolithiasis. Dehydration leads to proximal tubule resorption of sodium and calcium in an effort to expand the extracellular volume, but this paradoxically worsens hypercalcemia
- Hypercalcemia also affects the electric conduction pathways of the heart. Patients with elevated calcium concentrations have electrocardiographic changes marked by shortened QTc intervals. In addition, severe hypercalcemia can cause the Osborn, or J wave, seen at the tail end of the QRS complex, which usually is associated with hypothermia.
- Increased calcium concentrations also have been shown to cause pancreatitis

Central nervous system
- Circumoral and peripheral paraesthesia
- Muscle cramps
- Tetany
- Seizures
- Extrapyramidal manifestations: tremor, ataxia, dystonia
- Proximal myopathy
- Depression, anxiety, psychosis

Cardiovascular
- Arrhythmias
- Hypotension, inotrope unresponsiveness
- Prolonged QT intervals, T-wave inversion
- Loss of digitalis effect

Respiratory
- Apnoea
- Laryngospasm
- Bronchospasm

causes of hypocalcemia

Calcium chelation
- Alkalosis (increased binding of calcium by albumin)
- Citrate toxicity (calcium chelation)
- Hyperphosphataemia (calcium chelation, ectopic calcification, reduced Vit D3 activity)
- Pancreatitis (calcium soap formation, reduced parathyroid secretion)
- Tumour lysis syndrome (hyperphosphataemia)
- Rhabdomyolysis (hyperphosphataemia and reduced levels of calcitriol)

Hypoparathyroidism
- Hypo- and hypermagnesaemia
- Sepsis (decrease PTH secretion, calcitriol resistance, intracellular shift of calcium)
- Burns (decrease in PTH secretion)
- Neck surgery (removal of parathyroid gland, calcitonin release during thyroid surgery and hungry bone syndrome post parathyroidectomy)

Hypovitaminosis D
- Inadequate intake
- Malabsorption
- Liver disease (impaired 25-hydroxylation of cholecalciferol)
- Renal failure (impaired 1-hydroxylation of cholecalciferol, hyperphosphataemia)

Reduced bone turnover
- Osteoporosis
- Elderly
- Cachexia

Drug induced
- Phenytoin (accelerated metabolism of Vit D3)
- Diphosphonates (see 'hypercalcaemia')
- EDTA (calcium chelation)
- Ethylene glycol (formation of calcium oxalate crystals in the urine
- Cis-platinum (renal tubular damage leading to hypermagnesuria)
- Protamine
- Gentamicin (hypermagnesuria leads to hypomagnesaemia and hypocalcaemia)

causes of hypercalcaemia

Common causes of hypercalcaemia in the critically ill patient
- Complication of malignancy
  - Bony metastases
  - Humoral hypercalcaemia of malignancy
- Posthypocalcaemic hypercalcaemia
  - Recovery from pancreatitis[14]
  - Recovery from acute renal failure following rhabdomyolysis[31-35]
- Primary hyperparathyroidism
- Adrenal insufficiency[21,22]
- Prolonged immobilization[16-19]
- Disorders of magnesium metabolism
- Use of TPN[36]
- Hypovolaemia
- Iatrogenic calcium administration

Less common causes of hypercalcaemia in the critically ill patient
- Granulomatous diseases – sarcoidosis, tuberculosis, berylliosis
- Vit A & D intoxication
- Multiple myeloma
- Endocrine
  - Thyrotoxicosis
  - Acromegaly
  - Phaeochromocytoma
- Lithium – chronic therapy

causes of hypocalcaemic with metabolic acidosis

- Acute renal failure
- Tumour lysis
- Rhabdomyolysis
- Pancreatitis
- Ethylene glycol poisoning
- Hydrofluoric acid intoxication

symptoms of hypocalcaemia

- Early symptoms of hypocalcemia include perioral numbness, paresthesias, muscle cramps, and mild mental status changes such as irritability.
- As hypocalcemia becomes more severe, there can be neuromuscular and cardiac findings, including Chvostek's and Trosseau's signs, as well as mental status changes, seizures, tetany, hypotension, and acute heart failure.
- Chvostek's sign is elicited by tapping the facial nerve anterior to the ear, which produces spasm of the muscles of the face; it has been shown to be positive in 10-30% of people with normal calcium concentrations.
- Trousseau's sign is positive when pressure on the wrist induced by inflation of a blood pressure cuff for 3-5 mins or tapping on the median nerve induces carpal spasm.
- Acute hypocalcemia decreases cardiac function by lengthening phase 2 of the cardiac action potential, which results in prolongation of the ST segment and the QT interval on electrocardiogram and can lead to VT
- Hypocalcemia can lead to cardiac failure, and this can be reversed with administration of calcium.

Cardiovascular
- Hypotension
- Arrhythmias
- Digitalis sensitivity
- Catecholamine resistance

Urinary system
- Nephrocalcinosis
- Nephrolithiasis
- Tubular dysfunction
- Renal failure

Gastrointestinal
- Anorexia/nausea/vomiting
- Constipation
- Peptic ulcer
- Pancreatitis

Neuromuscular
- Weakness

Neuropsychiatric
- Depression
- Disorientation
- Psychosis
- Coma
- Seizures

management of hypercalcemia.

Fluids and diuretics
- In the setting of hypercalcemia, initial management is medical and promotes the renal excretion of calcium.
- Intravenous fluids, preferably normal saline, are administered at a rapid rate (200-300 mL/hr) to reverse intravascular volume contraction and promote renal excretion of calcium.
- Loop diuretics are added to the regimen to reduce the risk of volume overload and inhibit calcium resorption in the loop of Henle. Patients with renal failure often cannot tolerate this large volume resuscitation; instead, they should be dialyzed with low-calcium dialysate.

Steroids
- Steroids lower calcium by inhibiting the effects of vitamin D. They also have been shown to decrease intestinal absorption of calcium, increase renal calcium excretion, and inhibit osteoclast-activating factor.
- Steroids are particularly effective in the setting of hypercalcemia secondary to granulomatous diseases, where hypercalcemia stems from vitamin D toxicity. The initial dose of hydrocortisone is 200-400 mg intravenously per day for 3-5 days.
- Steroids are ineffective in most cases of hypercalcemia associated with malignancy.

Calcitonin
- Calcitonin acts quickly (within 24-48 hrs) to lower serum calcium concentrations and is more effective when used in combination with steroids.

Bisphosphonates
- Bisphosphonates are pyrophosphate analogs that have a high affinity for hydroxyapatite in bone. They potently inhibit osteoclast activity for up to a month.
- In the hypercalcemia of malignancy, pamidronate (90 mg intravenously) or zoledronic acid (4 mg intravenous initial treatment, 8 mg on retreatment) normalizes calcium concentrations in most patients
- A single dose of a bisphosphonate lowers calcium concentrations, although recent evidence suggests that zoledronic acid might become the bisphosphonate of choice because of its rapid onset of action and its ability to lengthen the time to relapse two-fold; however, there also has been an association between zoledronic acid and compromised renal function.

Surgery
- If a patient is diagnosed with primary hyperparathyroidism, parathyroidectomy can achieve cure.

general
- Mild asymptomatic hypercalcemia discovered on preoperative assessment should be evaluated further, whereas symptomatic hypercalcemia requires more urgent therapy.
- Pharmacologic agents associated with hypercalcemia should be discontinued; specifically, digoxin potentiates arrhythmias in the setting of hypercalcemia and should be discontinued.

management of hypocalcaemia

- Patients with hypocalcaemia who are clinically stable can receive oral calcium.
- In emergent situations, 100-200 mg of calcium can be given intravenously as a bolus, and a central vein should be used whenever possible. One milliliter of calcium chloride provides 27 mg of elemental calcium, and 1 mL of calcium gluconate gives 9 mg.
- Calcium chloride elevates the calcium concentration after plasmapheresis for longer periods and is the historically favored calcium replacement because there is a higher dose of elemental calcium in 1mL.

Preparation	Dosage	Elemental calcium
Calcium gluconate	10 ml	93 mg (2.3 mmol)
Calcium chloride	10 ml	272 mg (6.8 mmol)

indications for calcium administration:

Absolute
- Symptomatic hypocalcaemia
- Ionized Ca <0.8 mmol/l
- Hyperkalaemia
- Ca channel blocker overdose

Relative
- Betablocker overdose
- Hypermagnesaemia
- Hypocalcaemia in the face of high inotrope requirement
- Massive blood transfusion post cardiopulmonary bypass to augment cardiac contractility

investigation of hypocalcaemia

Aetiology of hypocalcaemia	Clinical/biochemical patterns
Low serum albumin	Reduced total calcium, normal ionized calcium
Alkalosis	Normal total calcium, reduced ionized calcium
Hypomagnesaemia	Reduced ionized calcium and hypokalaemia
Pancreatitis	Hypocalcaemia, elevated serum lipase and glucose
Renal failure	Elevated blood urea nitrogen, elevated phosphate
Rhabdomyolysis	Hypocalcaemia, elevated phosphate, CK and urinary myoglobin
Tumour lysis syndrome	Hypocalcaemia, elevated phosphate, potassium and urate