Hypercalcemia
Diagnosis and Treatment

National Nurse Practitioner Symposium
Keystone, CO
July 10, 2021

Michael T. McDermott MD
Director, Endocrinology and Diabetes Practice
University of Colorado Hospital

Disclosure

- Michael McDermott MD has no conflicts or disclosures in regard to this presentation.
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.

Learning Objectives

- Explain the physiology of serum calcium regulation and review the disorders that cause hypercalcemia
- Develop strategies for evaluation of people who have hypercalcemia
- Discuss the treatment options for the multiple types of hypercalcemia

Calcium Metabolism
Calcium Regulating Hormones

- Parathyroid Hormone 
- 1,25 (OH)2 Vitamin D 
- Calcitonin 

Calcium Metabolism
Calcium Regulating Organs

- Bone 
- Kidney 
- Intestine 

Calcium Regulation
Maintain Serum Calcium Within Narrow Range

Calcium Regulation

Maintain Serum Calcium Within Narrow Range

Upper Normal Limit — 10.5 mg/dl

↓ PTH, ↓ 1,25 Vitamin D, ↑ Calcitonin

10.0 mg/dl — Calcium Lowering Mechanisms Activated

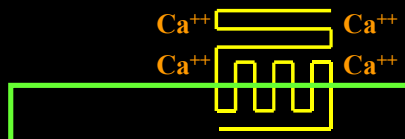
9.5 mg/dl

9.0 mg/dl — Calcium Raising Mechanisms Activated

↑ PTH, ↑ 1,25 Vitamin D, ↓ Calcitonin

Lower Normal Limit — 8.5 mg/dl

Calcium Sensor Receptor



Parathyroid Cell - PTH
Parafollicular C-Cell - Calcitonin
Renal Tubular Cell - Ca Excretion

Vitamin D Regulation

Skin → Vitamin D ← Diet

D3 Cholecalciferol

D2 Ergocalciferol
D3 Cholecalciferol

25 OH Vitamin D — Vitamin D Storage Form

PTH →

1,25 (OH)2 Vitamin D — Active Vitamin D

↑ Intestinal Calcium and Phosphorus Absorption

Hypercalcemia

Causes

- 1º Hyperparathyroidism*
- Hypercalcemia of Malignancy
- Granulomatous Disease
- Vitamin D Intoxication
- Vitamin A Intoxication
- Hyperthyroidism
- Thiazide Diuretics
- Milk-Alkali Syndrome
- Immobilization
- Adrenal Insufficiency
- Acute Renal Failure
- Familial Hypocalciuric Hypercalcemia*

* ↑ PTH

↓ PTH – All Others

Hypercalcemia

Classification

PTH Dependent
- Primary Hyperparathyroidism
- Lithium Induced Parathyroid Hyperplasia
- Familial Hypocalciuric Hypercalcemia (CaSR Mutation)

PTHrp / Cytokine Dependent
- Hypercalcemia of Malignancy

25 OH Vit D Dependent
- Vitamin D Toxicity

1, 25 (OH)2 Vit D Dependent
- Sarcoidosis
- Lymphomas
- Granulomatous Diseases
- Cyp24A1 Mutations

Other Mechanisms
- Milk Alkali Syndrome
- Hyperthyroidism
- Thiazide Diuretics
- Acute Renal Failure
- Adrenal Insufficiency
- Vitamin A Intoxication
- Immobilization

Hypercalcemia

Evaluation

History Physical Exam → PTH Creatinine, CO2, Phosphorus

PTH ↑ / Nl → Primary Hyperparathyroidism

Lithium Induced Parathyroid Hyperplasia

Familial Hypocalciuric Hypercalcemia

Cr ↑ / CO2 ↑ → Milk-Alkali Syndrome → Vitamin D Toxicity → Cancer Search

PTH ↓ → 25 Vitamin D → PTHrp ↑ → 1,25 Vitamin D → Sarcoidosis, Lymphoma, Granulomatous Inf/Dz, Cyp24A1 Mutation

PTH ↓ → PTHrp → PTHrp ↓ → SPEP/UPEP → Multiple Myeloma

Case

18 year old male presents for an 18 month history of right-side facial swelling and a left hard palate mass.

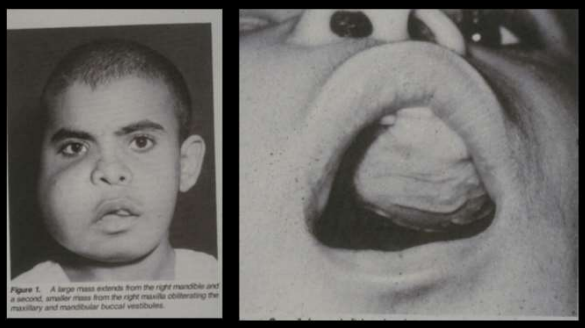
PE: large firm right facial mass

large firm left hard palate mass

Lab: Calcium 17.0 mg/dl Phos 2.0 mg/dl

Creatinine 0.5 mg/dl Albumin 3.9 g/dl

Case



Lab: Calcium 17.0 mg/dl Phosphorus 2.0 mg/dl
Creatinine 0.5 mg/dl Albumin 3.9 g/dl

Case

Repeat Labs:
Calcium 17.2 mg/dl (nl: 8.5-10.3)
PTH 108 pg/ml (nl: 10-65)

Biopsy of Right Maxillary Mass:
Brown Tumor of Hyperparathyroidism

Parathyroid Surgery:
2.0 x 1.5 cm Left Inferior Adenoma

Primary Hyperparathyroidism
Classification

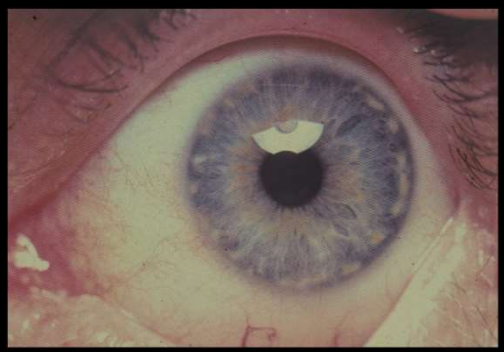
- PTH Adenoma 85%
- PTH Hyperplasia 15%
- PTH Carcinoma < 1%

Primary Hyperparathyroidism
Clinical Features

- Asymptomatic (> 50%)
- Skeletal Disease
- Kidney Disease
- Gastrointestinal Disease
- Psychiatric Disease
- Arthritis
- Muscle Weakness
- Band Keratopathy
- Hypertension
- Anemia

Classic Symptoms
Bones, Stones, Groans, Moans

Hyperparathyroidism
Band Keratopathy



Hyperparathyroidism
Brown Tumor (Osteoclastoma)

Hyperparathyroidism
Osteitis Fibrosa Cystica

Hyperparathyroidism
Chondrocalcinosis

Primary Hyperparathyroidism
Diagnosis

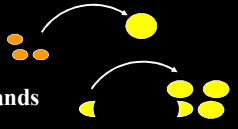
- ↑ Serum Calcium
- ↓ Serum Phosphate
- ↑ / nl Serum PTH

Parathyroid Imaging – Localizing Only
Does Not Diagnose or Rule Out
Primary Hyperparathyroidism

Primary Hyperparathyroidism
Treatment

Surgery

- Adenoma - 1 Gland
- Hyperplasia - 3 1/2 Glands



Calcimimetic Drug (Cinacalcet)

Anti-Resorptive Bone Drug

- Bisphosphonate

Primary Hyperparathyroidism
When Surgery is Recommended

- **Serum Calcium** > 1 mg/dl Above Normal
- **Urine Calcium** > 400 mg / 24 hours
- **Creatinine Clearance** < 60 ml/min
- **BMD T-Score** ≤ -2.5 or Fragility Fracture
- **Kidney Stones**
- **Age** < 50 Years

Bilezikian J, J Clin Endo Metab 2014; 99:3561-9

Primary Hyperparathyroidism
Familial

Familial 10%

- MEN I
- MEN IIA
- Familial HPT

Familial: Always Hyperplasia

Multiple Endocrine Neoplasia I

- Pituitary Tumors
- Pancreatic Islet Tumors
- Parathyroid Hyperplasia

Germline Mutation: Menin Gene

Multiple Endocrine Neoplasia IIA

- Medullary Thyroid Carcinoma
- Pheochromocytoma
- Parathyroid Hyperplasia

Germline Mutation: Ret Gene (GDNF receptor)

Case

64 year old woman with ↑ calcium on routine screen. She has not been experiencing any symptoms.
Lab: Ca 10.6 Phos 3.1 PTH 45 (nl: 10-65)
Urine Ca 210 mg/24 hr. (nl, 100-300)
BMD: Spine T-score -0.3 Hip T-score +0.5

What is the cause of her hypercalcemia?
1. Hypercalcemia of Malignancy
2. Familial Hypocalciuric Hypercalcemia
3. Primary Hyperparathyroidism
4. Secondary Hyperparathyroidism

Case

64 year old woman with ↑ calcium on routine screen. She has not been experiencing any symptoms.
Lab: Ca 10.6 Phos 3.1 PTH 50 (nl: 10-65)
Urine Ca 210 mg/24 hr. (nl, 100-300)
BMD: Spine T-score -0.3 Hip T-score +0.5

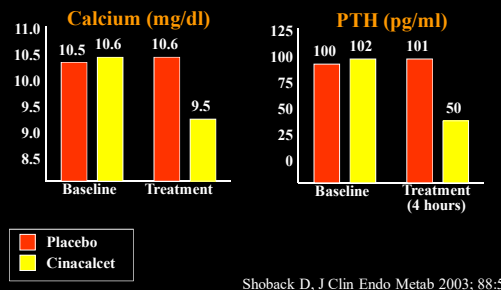
What management do you recommend?
1. Observation with monitoring every 6-12 months
2. Parathyroid scan and surgery
3. Calcimimetic therapy (Cinacalcet) to lower PTH/Ca
4. Bisphosphonate therapy to prevent bone loss

Primary Hyperparathyroidism
Non-Surgical Management

- Observation with Calcium/Vitamin D Rx
- Calcimimetic Drug – Cinacalcet (Sensipar)*
- Anti-Resorptive Drug – Bisphosphonate*

Primary Hyperparathyroidism
Calcimimetic Therapy

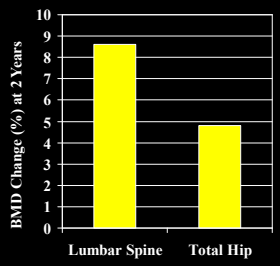
RCT: 22 subjects with **Primary Hyperparathyroidism**
Cinacalcet or Placebo for 15 days



Shoback D, J Clin Endo Metab 2003; 88:5644-9

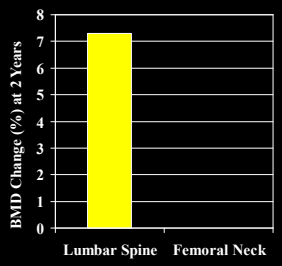
Primary Hyperparathyroidism
Bisphosphonate Therapy

26 patients with HPTH (age: 67-81)
Alendronate vs. No Therapy x 2 years



Rossini M, JBMR 2001; 16:113

32 patients with HPTH (mean age: 66)
Alendronate vs. No Therapy x 2 years



Parker CR, JCEM 2002; 87:4482

Primary Hyperparathyroidism
Mild Asymptomatic

Monitor:

Measurement	Frequency
Serum Calcium	Every 6 Months
Serum Creatinine	Every Year
Bone Density*	Every Year

*Spine, Hip and Mid-Radius

Bilezikian J, J Clin Endo Metab 2009; 94:335-9

Primary Hyperparathyroidism
Mild Asymptomatic

Calcium and Vitamin D Intake:

Nutrient	Amount*
Calcium	1,000-1,200 mg/day
Vitamin D	400-600 Units/day

***Monitor serum calcium levels.**
If calcium increases significantly, consider surgery.

Bilezikian J, J Clin Endo Metab 2009; 94:335-9

Case

A 58 year old woman complains of fatigue and "fuzzy thinking". She has recently passed 3 kidney stones.
Lab: Ca 12.4 Phos 2.6 PTH 72 (nl: 10-65)
Parathyroid (Sestamibi) Scan: Negative
Neck Ultrasound: No Parathyroid Adenoma Seen

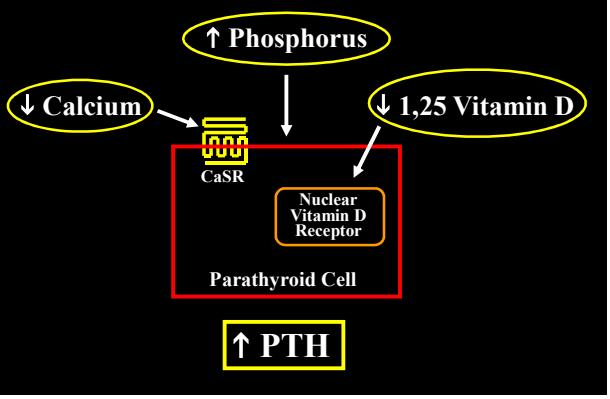
What management do you recommend?
1. Observation with monitoring every 6-12 months
2. Referral to an experienced neck surgeon
3. Calcimimetic therapy (Cinacalcet) to lower PTH/Ca
4. Bisphosphonate therapy to prevent bone loss

Primary Hyperparathyroidism
When Imaging is Negative

- Parathyroid Surgery by Experienced Surgeon
- Calcimimetic Drug (Cinacalcet)
- Anti-Resorptive Bone Drug
  - Bisphosphonate, Denosumab

Bilezikian J, J Clin Endo Metab 2014; 99:3561-9

Secondary Hyperparathyroidism



Case

A 69 year old man complains of recent weakness, nausea, vomiting and a chronic worsening cough.

PE: BP 134/85 P 86 Ht 5'11" Wt 198 lb

Lab: Ca 15.2 Cr 1.1 CO2 24 Phos 3.7
PTH < 1 pg/ml

What additional testing do you recommend?

1. PTHrp
2. TSH and Free T4
3. CT scan abdomen
4. 24-hour urine calcium and creatinine

Case

A 69 year old man complains of recent weakness, nausea, vomiting and a chronic worsening cough.

PE: BP 134/85 P 86 Ht 5'11" Wt 198 lb

Lab: Ca 15.2 Cr 1.1 CO2 24 Phos 3.7
PTH < 1 pg/ml
PTHrp 38 pmol/L (nl: 0-3)

CXR: right hilar mass

What is the most likely cause of hypercalcemia?

1. Sarcoidosis
2. Tuberculosis
3. Lung Cancer
4. Multiple Myeloma

Hypercalcemia of Malignancy

Tumor Types

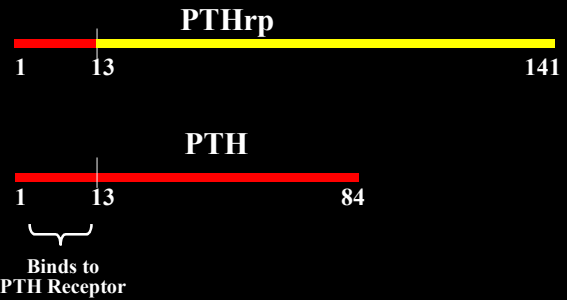
- Lung (Squamous Cell, esp.)
- Breast
- Head and Neck
- Multiple Myeloma
- Lymphomas
- Kidney
- Bladder
- Ovarian
- Pancreatic

Hypercalcemia of Malignancy

Mediators

- PTH Related Peptide (PTHrp)
- 1,25 (OH)2 Vitamin D
- Transforming Growth Factors (TGFβ)
- Tumor Necrosis Factor (TNF)
- Interleukin 1, Interleukin 6
- RANK-L
- DKK-1

Parathyroid Hormone Related Peptide



Hypercalcemia of Malignancy
Diagnosis

- ↑ Serum Calcium
- ↓ Serum PTH (very low / not detected)
- ↑ Serum PTHrp (+/-)
- ↑ Serum 1,25 (OH)2 Vitamin D (+/-)

Hypercalcemia of Malignancy
Emergency Treatment

Promote Urine Calcium Excretion
- Saline Infusion (+/- Loop Diuretic)

Inhibit Bone Resorption (IV/SQ)
- Bisphosphonates
- Denosumab
- Calcitonin

Remove Calcium from Circulation
- Hemodialysis

Case

A 72 year old woman has an elevated serum calcium on pre-op labs before elective surgery.

PMH: GERD, Osteopenia **Meds:** Calcium and D supplements
PE: BP 139/80 P 82 Ht 5'5" Wt 142 lb
Lab: Ca 14.1 mg/dl Creat 7.1 mg/dl CO2 37 mEq/L
PTH < 1 pg/ml (nl: 10-65)
PTHrP 1.8 pmol/L (nl: 0-3)
25 Vitamin D 85 ng/ml (nl: 30-100)

What is the most likely cause of hypercalcemia?
1. Sarcoidosis
2. Tuberculosis
3. Vitamin D Toxicity
4. Milk Alkali Syndrome

Milk Alkali Syndrome

Diagnostic Triad
- Hypercalcemia
- Metabolic Alkalosis
- Renal Insufficiency

Associated with the ingestion of excess calcium and absorbable alkali, most commonly calcium carbonate.

Medarov BI. Mayo Clin Proc 2009; 84(3): 261-7
Patel AM. Nutrients 2013; 5(12):4880-93
Machado MC. J Clin Med 2015; 4(3):414-24

Milk Alkali Syndrome

Mechanism
Excess Calcium Intake → Hypercalciuria
Calcium Induced Diuresis → Volume Depletion, Renal Insufficiency and ↑ Renal Bicarbonate Absorption.

Treatment
Hydration
Stop Calcium and Vitamin D until Calcium Normal
Dialysis may be needed

Medarov BI. Mayo Clin Proc 2009; 84(3): 261-7
Patel AM. Nutrients 2013; 5(12):4880-93
Machado MC. J Clin Med 2015; 4(3):414-24

Case

A 40 year old woman has an elevated serum calcium on her annual check-up. Good general health.

PMH: Osteoarthritis **Meds:** Multivitamins and Supplements
PE: BP 120/84 P 72 Ht 5'5" Wt 134 lb
Lab: Ca 11.1 Cr 1.3 CO2 25 Phos 5.3
PTH < 1 pg/ml

What test is most likely to reveal the correct diagnosis?
1. PTHrp
2. TSH and Free T4
3. 25 OH Vitamin D
4. Serum Protein Electrophoresis

Case

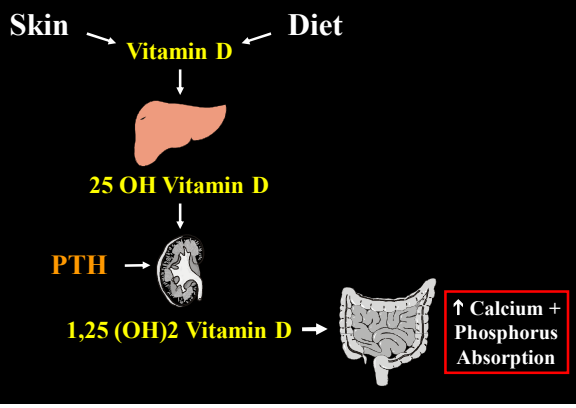
A 40 year old woman has an elevated serum calcium on her annual check-up. Good general health.

PMH: Osteoarthritis Meds: Multivitamins and Supplements

PE: BP 120/84 P 72 Ht 5'5" Wt 134 lb

Lab: Ca 11.1 Cr 1.3 CO2 25 Phos 5.3
PTH < 1 pg/ml
25 OH Vitamin D 182 ng/ml (nl: 30-100)

Vitamin D Metabolism and Action



Vitamin D Toxicity with Hypercalcemia

Mechanism

Vitamin D Excess → Increased GI Absorption of Calcium and Phosphorus

Treatment

Hydration
Stop Vitamin D Intake until Calcium and 25 OH Vitamin D are Normal
Loop Diuretic Can be Used

Tebben PJ. Endo Rev 2016; 37(5): 521-47

Case

A 45 year old man with dyspnea on exertion.

PMH: Hep C, Bipolar Meds: α Interferon, Ribavirin, Lithium

Dietary Ca: 600 mg/day No supplements

PE: Ht 5'10" 185 lb Diffuse rales

Lab: Ca 12.4 Cr 1.2 CO2 23 PTH 4 pg/ml
PTHrP 1.8 pmol/L (nl: 0-3)
25 Vitamin D 43 ng/ml (nl: 30-100)

What test is most likely to reveal the correct diagnosis?

1. Lithium Level
2. 1,25 (OH)2 Vitamin D
3. Interferon Level
4. Serum Protein Electrophoresis

Case

A 45 year old man with dyspnea on exertion.

PMH: Hep C, Bipolar Meds: α Interferon, Ribavirin, Lithium

Dietary Ca: 600 mg/day No supplements

PE: Ht 5'10" 185 lb Diffuse rales

Lab: Ca 12.4 Cr 1.2 CO2 23 PTH 4 pg/ml
PTHrP 1.8 pmol/L (nl: 0-3)
25 Vitamin D 43 ng/ml (nl: 30-100)
1,25 (OH)2 Vitamin D 152 pg/ml (nl: 15-75)

What would you order now?

1. CT Abdomen
2. Chest X-ray
3. TB Skin Test
4. MRI Brain

Case

A 45 year old man with dyspnea on exertion.

PMH: Hep C, Bipolar Meds: α Interferon, Ribavirin, Lithium

Dietary Ca: 600 mg/day No supplements

PE: Ht 5'10" 185 lb Diffuse rales

Lab: Ca 12.4 Cr 1.2 CO2 23 PTH 4 pg/ml
PTHrP 1.8 pmol/L (nl: 0-3)
25 Vitamin D 43 ng/ml (nl: 30-100)
1,25 (OH)2 Vitamin D 152 pg/ml (nl: 15-75)

CXR: hilar adenopathy and diffuse interstitial lung disease

What would you order now?

1. Bronchoscopy with biopsy of hilar nodes
2. Histoplasmosis antibody titers
3. Chest CT scan
4. TB Skin Test

Case

A 45 year old man with dyspnea on exertion.

PMH: Hep C, Bipolar **Meds:** α Interferon, Ribavirin, Lithium

Dietary Ca: 600 mg/day No supplements

PE: Ht 5'10" 185 lb Diffuse rales

Lab: Ca 12.4 Cr 1.2 CO2 23 PTH 4 pg/ml
PTHrP 1.8 pmol/L (nl: 0-3)
25 Vitamin D 43 ng/ml (nl: 30-100)
1,25 (OH)2 Vitamin D 152 pg/ml (nl: 15-75)

CXR: hilar adenopathy and diffuse interstitial lung disease

Biopsy: non-caseating granulomas c/w sarcoidosis

1,25 (OH)2 Dependent Hypercalcemia

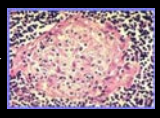
Cause	Frequency
Sarcoidosis	50%
Lymphoma	17%
Granulomatous Infection	8%
Granulomatous Disease (Other)	4%
Idiopathic	3%

Donovan P. J Clin Endocrinol Metab 2013; 98:4023-9

Hypercalcemia due to Sarcoidosis

Mechanism

Excess 1,25 (OH)2 Vitamin D Production by Granulomatous Tissue (1α hydroxylase)

25 OH Vitamin D →  → 1,25 (OH)2 Vitamin D

1 α hydroxylase

↑ Intestinal Calcium + Phosphorus Absorption

Tebben PJ. Endo Rev 2016; 37(5): 521-47

Hypercalcemia due to Sarcoidosis

Treatment

Hydration

Glucocorticoids

- Anti-Inflammatory Effect

Hydroxychloroquine

- Anti-Inflammatory Effect

Ketoconazole

- Inhibits 1 Alpha Hydroxylase

Limit Vitamin D Intake

Paromothyan S. JAMA 2002; 287:1301-1307
Adams J. J Clin Endocrinol Metab 1990; 70:1090-5
Sharma O. Current Opinion in Pulmonary Med 2000; 6:442-447

Hypercalcemia due to Infection

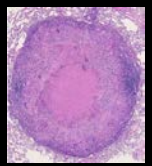
Organisms

- Mycobacterium Tuberculosis
- Mycobacterium non-TB
- Cat Scratch Disease
- Coccidioidomycosis
- Histoplasmosis
- Cryptococcosis
- Pneumocystis
- Leprosy
- COVID 19

Hypercalcemia due to Infection

Mechanism

Excess 1,25 (OH)2 Vitamin D Production by Granulomatous/Inflammatory Tissue (1α hydroxylase)

25 OH Vitamin D →  → 1,25 (OH)2 Vitamin D

1 α hydroxylase

↑ Intestinal Calcium + Phosphorus Absorption

Tebben PJ. Endo Rev 2016; 37(5): 521-47

Hypercalcemia due to Infection
Treatment

- **Hydration**
- **Treat the Infection**
- **Hydroxychloroquine**
  - **Anti-Inflammatory Effect**
- **Ketoconazole**
  - **Inhibits 1 Alpha Hydroxylase**
- **Limit Vitamin D Intake**

Paromothyan S. JAMA 2002; 287:1301-1307
Adams J. J Clin Endocrinol Metab 1990; 70:1090-5
Sharma O. Current Opinion in Pulmonary Med 2000; 6:442-447

Case

A 32 year old woman presents for an insurance exam.

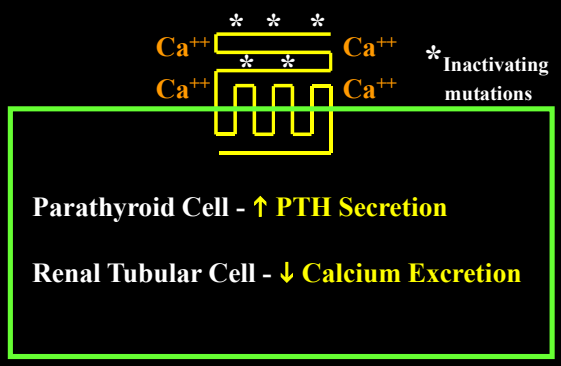
FH: Mother and Sister have elevated calcium

Lab: Calcium 11.0 Phos 4.1 PTH: 67 pg/ml (nl: 10-65)

Urine Ca 32 mg/24 hr. (nl: 100-300)

Calcium/Creatinine Clearance Ratio: 0.005

Calcium Sensor Receptor



Parathyroid Cell - ↑ PTH Secretion

Renal Tubular Cell - ↓ Calcium Excretion

Familial Hypocalciuric Hypercalcemia
Diagnosis

- ↑ Serum Calcium (mild)
- ↑ Serum PTH (mild)
- ↓ Urinary Calcium
  - ↓ Urine Calcium / Creatinine Clearance Ratio
  - (Uca x Pcr / Pca x Ucr) < .01

Familial Hypocalciuric Hypercalcemia
Treatment

- **No Treatment Necessary**
- **Avoid Surgery**

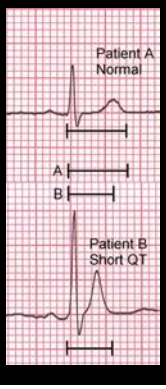
Hypercalcemic Crisis
Definition

Serum Calcium ≥ 14 mg/dl

Clinical Features
Dehydration
Nausea, Vomiting
Acute Kidney Injury
Mental Status Changes
Cardiac Dysrhythmias
ECG Changes

Hypercalcemic Crisis

ECG Changes



Short QTC

Hypercalcemic Crisis

Treatment Options

Medication	Mechanism	Onset	Duration
Normal Saline	↑ Renal Ca Loss	Hours	Short
Loop Diuretics	↑ Renal Ca Loss	Hours	Short
Calcitonin	↓ Bone Resorption	4-6 Hrs	48 Hrs
Bisphosphonates	↓ Bone Resorption	24-72 Hrs	2-4 Wks
Denosumab	↓ Bone Resorption	4-10 Days	4-15 Wks
Glucocorticoids	↓ Intest. Ca Absorption ↓ 1,25 Vit D Production by Mononuclear Cells	2-5 Days	Weeks
Calcimimetics	↓ PTH Production	-3 Days	Short
Dialysis (low Ca)	Removes Ca	Hours	Short

Shane E. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (6th Ed.) Am Soc Bone Min Research 2006; 179

Hypercalcemic Crisis

Treatment Recommendations

PTH / PTHrp Mediated

- Normal Saline Infusion
  - 200-300 ml/hr to keep urine output at 100-150 ml/hr
- Calcitonin SQ
  - 4 IU/kg; repeat 4-8 IU/kg every 6-12 hour for 48 hrs
- Zoledronic Acid IV, 4 mg
- Dialysis (Low Ca Bath)

Vitamin D Mediated

- Glucocorticoids
- Normal Saline Infusion
  - 200-300 ml/hr to keep urine output at 100-150 ml/hr
- Calcitonin SQ
  - 4 IU/kg; repeat 4-8 IU/kg every 6-12 hour for 48 hrs
- Zoledronic Acid IV, 4 mg
- Dialysis (Low Ca Bath)

Treat the Underlying Cause

Thank You