Hypercalcemia &
Parathyroid Disorders

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Objectives

• Review diagnostic workup for hypercalcemia
• Review management of primary hyperparathyroidism
• Review management of hypoparathyroidism
Approaching Hypercalcemia

• Broad differential diagnosis for hypercalcemia
  • PTH-dependent and PTH-independent hypercalcemia
  • 90% Rule
• Clinical acumen and focused testing is key to quick and cost-effective evaluation
  – Medical History
  – Two-tiered approach to diagnostic testing in the outpatient setting
# Hypercalcemia: Differential Diagnosis

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<th>PTH Independent</th>
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<td>Milk-Alkalai Syndrome</td>
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<td>Dehydration</td>
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Hypercalcemia: 90\textsuperscript{th} Percentile

**Primary Hyperparathyroidism**
- Asymptomatic or mild symptoms
- Lower calcium
- Chronic hypercalcemia
- Outpatient setting

**Hypercalcemia of Malignancy**
- Recognized malignancy
- More symptomatic
- Higher calcium
- Hospital setting
Primary Hyperparathyroidism

- Excessive production of PTH by parathyroid glands
  - Single adenoma: 90%
  - Double adenoma: 5%
  - Multi-gland hyperplasia: 5%
- PTH Actions
  - Bone: increased mobilization of calcium via osteoclasts
  - Kidney
    - Increases production of $1,25(\text{OH})_2\text{D}$
    - Increases tubular reabsorption of calcium
    - Decreases tubular reabsorption of phosphate
Primary Hyperparathyroidism

• Symptoms
  – 80% asymptomatic or mild
  – Non-specific
    • fatigue, cognitive, depression, neuromuscular
    • sometimes only realized post-parathyroidectomy
  – Classic
    • polyuria, nephrolithiasis
    • neuromuscular, bone pain, musculoskeletal
    • abdominal pain, constipation, anorexia, nausea
    • neuropsychiatric symptoms
Hypercalcemia of Malignancy

• 20-30% of cancer patient have hypercalcemia
• Most common malignancies
  – Breast Cancer
  – Lung Cancer
  – Multiple Myeloma
• Most have clinically evident disease, poor prognosis
• Treatment
  – IV bisphosphonates: zoledronic acid, pamidronate
  – Calcitonin – severe hypercalcemia
  – Steroids – selected cases
HOM: Mechanisms of Action

PTHrp

– 80% of HOM
– Binds to PTH receptor
– Increased mobilization of calcium from bone
– Increase reabsorption of calcium in renal tubule
  • Squamous Cell Ca (head, neck, lung)
  • Renal Cell Ca
  • Bladder Ca
  • Breast Ca
  • Ovarian Ca
HOM: Mechanism of Action

Osteolytic Bone Lesions

- 20% of HOM
- Production of cytokines which activate osteoclasts
- Increased mobilization of calcium from bone
  - Breast Ca
  - Multiple Myeloma
  - Leukemia/Lymphoma
HOM: Mechanism of Action

- 1,25-Dihydroxy D
  - Increased production by malignant lymphocytes and macrophages
  - Absorptive hypercalcemia
  - Responds best to steroids
    - Hodgkins Ds
    - NHL
Outpatient Evaluation of Hypercalcemia

• History
  – Symptom severity & duration
  – Duration and severity of hypercalcemia
  – Associated Conditions
  – FHx
  – Medications

• Two-Tiered Diagnostic Testing
  – Initial Workup
  – Expanded Workup (if necessary)
Hypercalcemia: Initial Workup

- Chemistry
  - Calcium
  - Albumin
  - Liver chemistry
  - Renal function
  - Electrolytes
- CBC
- TSH

- Ionized calcium
- Phosphorus
- Intact PTH
- 24 hour urine calcium
- 25-OH-D
Diagnosis Confirmed . . .

Primary Hyperparathyroidism

– Elevated calcium, ionized calcium
– PTH
  • Elevated
  • Upper normal range in 10-20% of PHP
– 24-hour urine calcium elevated
– Phosphorus
  • Usually low
– 25-OH-D
  • usually low in PHP
Diagnosis Confirmed . . .

Familial Hypercalcemic Hypocalciuria (FHH)

- Mutation of calcium sensor: calcium resistance
- Lifelong hypercalcemia with positive FHx
- Elevated calcium, ionized calcium
- PTH: high normal to mildly elevated
- 24-hour urine calcium: low
- Genetic testing available
Hypercalcemia: Expanded Workup

• PTHrp
• 1,25-dihydroxy D
• Serum ACE
• SPEP/UPEP
• Vitamin A

• IF clinically indicated
  – Chest Imaging
  – Cortisol/ACTH
  – Catecholamines
  – IGF-1
  – Genetic testing for FHH
Secondary Workup

• HOM
  relevant medical history
  ± elevated PTHrp
  ± elevated 1,25(OH)$_2$D

• Granulomatous Disease (TB, sarcoidosis, etc)
  relevant medical history and diagnostic imaging
  elevated angiotensin converting enzyme
  ± elevated 1,25(OH)$_2$D
Management of Primary Hyperparathyroidism
Additional Testing

• DEXA Scan
  – increased incidence of bone loss
  • Cortical Bone > Trabecular Bone
  • (wrist, hip > spine)
  – increased incidence of fractures
  • paradoxically higher in the spine!

• Localization of Disease
  – biochemically confirmed disease
  – operative planning
Localization of Disease

• Neck Ultrasound
  – characteristics: hypoechoic, homogeneous, polar artery
  – First-line investigation
  – highly cost-effective
  – highly operator-dependent
  – reduced sensitivity if
    • co-existing thyroid disease (20-30%)
    • obesity
    • ectopic glands
Localization of Disease

• Sestamibi Scintigraphy
  – technetium-99m-methoxyisobutylisonitrile (99m-Tc-sestamibi or MIBI)
  – identifies hyperfunctioning parathyroid tissue, but little anatomical detail
  – negative scan in up to 25%
    • small size
    • superior location
    • multigland disease
    • co-existing thyroid disease
Localization of Disease

• Sestamibi SPECT (MIBI-SPECT)
  – 3 dimensional MIBI scintigraphy
  – improves performance of MIBI scanning
    • anatomic location relative to thyroid
    • better for ectopic glands
    • still can miss multigland disease

• MIBI-SPECT/CT Fusion
  – adds benefits of CT to discern other anatomical landmarks
Localization of Disease

• Subtraction Thyroid Scan
  – dual isotope scanning
    • MIBI: parathyroid
    • $^{123}$I or 99mTc-pertechnetate (thallium): thyroid & parathyroid glands
  – digital subtraction of thyroid image shows parathyroid pathology
Localization of Disease

- 4 Dimensional CT
  - CT for anatomic visualization of neck
  - 4th dimension makes use of rapid uptake and washout of contrast by parathyroid adenomas
  - disadvantage: > 50-fold greater radiation exposure to thyroid vs MIBI
    - radiation to thyroid increases risk of thyroid cancer
    - use selectively in young patients
Localization of Disease

• MRI
  – adenoma
    • intermediate to low signal intensity on T1
    • high signal intensity on T2
  – cervical nodes look similar and may limit usefulness
  – doesn’t require iodinated contrast material

• PET/CT
  – PET/CT fusion technology that uses 11C-methionine is a radiotracer to localizes pathological parathyroids (MET-PET-CT)
Indications for Surgery

Asymptomatic Patients with 1 or more of the following:

- < 50 yrs of age
- Serum calcium > 1 mg/dl over upper limit normal
- Osteoporosis
  - vertebral fracture by CT, MRI or VFA
  - DEXA T score < -2.5 in total hip, femoral neck, lumbar spine or distal 1/3 radius
- Nephrolithiasis or nephrocalcinosis
- Urine calcium > 400 mg/day
- eGFR < 60
Surgical Management

Minimally Invasive Parathyroidectomy
- pre-op localization generally recommended for surgical planning
- experienced parathyroid surgeon
- intraoperative PTH monitoring

Reoperation for Recurrent or Persistent Disease
- needed in 5-10% of patients
- pre-op localization is important
  - imaging
  - +/- FNA aspiration for PTH
- experienced parathyroid surgeon
- increased incidence of complications due to fibrosis from prior surgery
  - permanent hypoparathyroidism
  - RLN injury
  - unsuccessful surgery
Medical Management

Cinacalcet

- calcimimetic activates calcium receptor in parathyroid tissue
- decreases PTH secretion
- does not improve bone density
- favorable response rates in 75% of patients
- starting dose 30 mg po QD and increase as needed to 30-60 mg BID
- Side Effects - up to 35%
  - nausea/diarrhea
  - arthralgia/myalgia
- VERY expensive
- not the equivalent to a medical parathyroidectomy
Watchful Waiting

Surveillance
- monitor renal function, calcium - Q6-12months
- DEXA every two years

Preventive Measures
- adequate hydration to reduce nephrolithiasis
- regular exercise to minimize bone resorption
- moderate calcium intake (1000 mg/day)
- moderate vitamin D levels (20-30 ng/mL)
- avoidance hypercalcemic triggers
  - prolonged bedrest or inactivity
  - thiazide diuretics, lithium
  - excessive intake of calcium or vitamin D
  - volume depletion
Management of Hypoparathyroidism
Hypoparathyroidism Overview

Etiology

• post-surgical hypoparathyroidism
• polyglandular autoimmune syndrome 1
  – hypoparathyroidism
  – adrenal insufficiency
  – mucocutaneous candidiasis

Symptoms

• numbness, paresthesias
• muscle cramps, tetany
• seizures
• arrhythmia
Hypoparathyroidism Management

Emergency Management
• severe hypocalcemia
  – tetany, carpopedal spasm AND
  – serum calcium < 7.5 mg/dl
• IV calcium
  – 1-2 grams calcium gluconate (90-180 mg elemental calcium) in 50 ml
    5% dextrose over 10-20 minutes
  – often provides transitory relief of symptoms for 3-4 hrs
  – 11 grams of 10% calcium gluconate (990 mg elemental calcium/110 ml)
    in 5% dextrose (remove 110 ml 5% dextrose) = 1 mg/ml elemental calcium solution
    • infuse over 24 hrs (40 ml/hr)
• Oral Maintenance
  – initiate oral calcium 1-2 grams elemental calcium in divided doses (TID to QID)
  – initiate calcitriol 0.25-0.5 mcg BID
Hypoparathyroidism Management

Chronic Management - Calcium
• 1-2 grams of elemental calcium daily in divided doses
  – dosing with meals to improve absorption
• calcium citrate preferred for better absorption
  – 200 mg elemental calcium/gram
  – calcium citrate 600 mg
    • 2 tablets QID = 960 mg elemental calcium per day
• calcium carbonate less expensive
  – 400 mg elemental calcium/gram
• supplemental calcium PRN breakthrough symptoms
Hypoparathyroidism Management

Chronic Management - Calcitriol

- activated vitamin D (1,25-dihydroxy D)
- dispensed in 0.25 mcg and 0.5 mcg capsules
- starting dose 0.25 mcg BID
- titrate up to 0.5 mcg BID to QID
- dose with calcium to improve calcium absorption

**CAUTION**

- risk of hypercalcemia with higher doses
- always check serum calcium within 1 wk of changing dose
**Hypoparathyroidism Management**

**Monitoring Therapy**

- monitor serum calcium weekly after changes
- regular assessment of renal function and calcium once stable dosing is established (Q3-6months)
- target calcium: 8.0 to 8.9 mg/dl
- periodic assessment of urine calcium
  - 24 hr urine calcium > 300 mg/day
    - cut dose of calcium & calcitriol
    - consider therapy with HCTZ 25-50 mg QD to decrease urinary calcium
Chronic Management - recombinant human PTH (1-84)
• recently approved for chronic management of hypoparathyroidism
• reduces doses of calcium and calcitriol needed to maintain serum calcium
  – 55% of rhPTH patients cut calcitriol by > 50% (vs. 2.5% PBO)
  – 42% of rhPTH were able to stop calcitriol and were on < 500 mg of calcium (vs. 2.5% PBO)
• Risk Evaluation Mitigation Strategy (REMS)
  – rhPTH increased incidence of osteogenic sarcoma in rat models
    • both genders, dependent on dose and duration
    – risk in humans cannot be excluded
    • use only when benefits exceed risk
    • do not use in patients with higher risk of osteogenic sarcoma
      – Paget’s disease of bone
      – prior exposure radiation therapy to skeleton
      – open epiphyses: pediatric patients or young adults
      – unexplained elevation of alkaline phosphatase
Hypoparathyroidism Management

Chronic Management - recombinant human PTH (1-84)

• Risk Evaluation Mitigation Strategy (REMS)
  – rhPTH increased incidence of osteogenic sarcoma in rat models
    • both genders, dependent on dose and duration
    • genetically predisposed animals
  – risk in humans cannot be excluded
    • use only when benefits exceed risk
    • not for patients well controlled on calcium/calcitriol
    • do not use in patients with higher risk of osteogenic sarcoma
      – Paget’s disease of bone
      – prior exposure radiation therapy to skeleton
      – open epiphyses: pediatric patients or young adults
      – unexplained elevation of alkaline phosphatase
Hypoparathyroidism Management

Chronic Management - recombinant human PTH (1-84)

- starting dose 50 mcg SQ daily
  - cut calcitriol by 50% on initiation
  - weekly monitoring of serum calcium
- adjust dose of calcitriol as first priority
- adjust dose of calcium as second priority
- increase rhPTH (1-84) by 25 mcg QD every 4 weeks to max dose 100 mcg QD

<table>
<thead>
<tr>
<th>Serum calcium</th>
<th>Adjust 1st</th>
<th>Adjust 2nd</th>
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<tbody>
<tr>
<td>&gt; ULN</td>
<td>decrease or stop</td>
<td>decrease</td>
</tr>
<tr>
<td>&gt; 9 and &lt; ULN</td>
<td>decrease or stop</td>
<td>no change or stop (if off D)</td>
</tr>
<tr>
<td>8.0 to 9.0 mg/dL</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>&lt; 8 mg/dL</td>
<td>increase</td>
<td>increase</td>
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Hypoparathyroidism: Summary

- significant quality of life issues
  - large number of tablets/day
  - side-effects with
    - non-compliance
    - exercise
    - changes in routine
- frequent/consistent dosing of calcium and calcitriol is mainstay of therapy
- benefits of rhPTH (1-84) for inadequately controlled patients
  - decrease calcitriol dependence
  - decrease in supplemental calcium dose
- need to remember periodic surveillance of calcium, renal function and urinary calcium