Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. ■, no. ■, 1–25, 2017

1094-6950/■:1–25/$36.00
http://dx.doi.org/10.1016/j.jocd.2017.05.011

Tools for Enhancement and Quality Improvement of Peer Assessment and Clinical Care in Endocrinology and Metabolism

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Abstract

Members of the College of Physicians and Surgeons of Ontario Endocrinology and Metabolism Peer Review Network have been involved in a quality improvement project to help standardize the peer assessment of physicians practicing in endocrinology and metabolism. This has included developing state-of-the-art summaries of common endocrine problems by Canadian experts in endocrinology and metabolism. These tools have been developed in response to the educational needs, as identified by peer reviewers, of practicing endocrinologists in Ontario. These pedagogical tools aim not only to standardize the documentation of the clinical performance of endocrinologists but also to make the process more transparent and to improve the quality of patient care in Ontario. This article summarizes the project and also provides the tools developed for the endocrinology and metabolism section of the College of Physicians and Surgeons of Ontario.

Key Words: Endocrinology; metabolism; point-of-care recommendations; quality improvement resources; secondary osteoporosis.

Introduction

The College of Physicians and Surgeons of Ontario (CPSO) has a mandate to ensure and to improve the quality of physician practice. The peer assessment program is a key component of this, the purpose of which is to

> "Promote continuous quality improvement by providing physicians with feedback to validate

Received 04/20/17; Revised 05/16/17; Accepted 05/21/17.
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appropriate care and show opportunities for practice improvement"

Members of the CPSO Endocrinology and Metabolism Peer Review Network conduct peer assessments that include a review of the clinician's patient records and an interview with the clinician. Reflecting on past assessments, peer assessors have identified recurring deficiencies in the history, clinical examination, laboratory investigation, diagnosis, and management of endocrine disorders. Practicing clinicians have also requested simple algorithms and summaries that outline and highlight recent advances in practice that are easy to incorporate into clinical care. The Endocrinology and Metabolism Peer Assessment Redesign initiative has sought to enhance the consistency of peer assessor decision making regarding the quality of care provided and to increase the transparency of the peer assessment process.

These pedagogical tools have been developed in response to the above. The tools include key points to be documented in the history as well as key physical findings for each endocrine problem. The tools also provide guidance regarding appropriate laboratory investigations, as well as diagnostic criteria and practice pearls. Current useful references are provided for further review. The tools have been developed by experienced Canadian clinicians regarded as leaders in their respective areas of expertise. Common endocrine topics have been covered. Diabetes has not been covered as excellent practice support tools have been developed by the Canadian Diabetes Association.

Methods

The topics selected address clinical issues in which peer-assessed endocrinologists have sought guidance. Endocrinologists recognized by peer assessors as authorities intimately familiar with the relevant current literature in specific disease states were invited to develop *quality improvement resources* (QIRs). The content was based on clinical care guidelines or evidence-based reviews published in peer reviewed journals in the past 5 yr.

The tools are summaries and are intended to be used at point of care by the clinician. These tools will be updated every 3 yr by the lead expert authoring each specific module. The authors also provide management pearls addressing key pitfalls in the clinical assessment of these common conditions. As the QIRs themselves represent models of high-quality care on a given topic, the tools are focused on education and are not intended to describe minimum standards of practice. The tools will be posted on the CPSO website and will be widely available to all, including referring physicians. The tools will provide clinicians with a summary of what peer reviewers will be looking for when they review patient charts during a peer assessment. This should help to standardize the peer review process and make it more transparent for those being reviewed.

The QIRs address key components of assessment and management and include the following:

- History
- Physical examination
- Investigations (wisely chosen laboratory testing and imaging)
- Diagnostic criteria for the problem
- Pearls for management and common pitfalls in care to be avoided
- One or more key references

QIRs have been developed for the problems. Other topics may also be added in the future.

Evaluation

The tools have been reviewed and approved externally by the Canadian Society of Endocrinology and Metabolism. A pilot assessment of the clinical usefulness of the tools will be completed by obtaining feedback from peer assessors as well as peer-assessed endocrinologists and referring physicians.

In conclusion, these tools summarize advances in current knowledge and are designed to provide a practical checklist of key points to be addressed at the time of the clinical evaluation of a patient with one of the endocrine problems summarized. It is anticipated that these pedagogical tools will also help to standardize the peer review process and to make the process more transparent. These tools will also provide more material feedback by peer reviewers for those clinicians not familiar with this project.

QIRs have been developed with the collaboration and contributions of the following authors:

1. Addison's Disease (Primary Adrenal Insufficiency)
   Author: Donald Killinger, MD
2. Familial Hypercholesterolemia
   Authors: Tisha Joy, MD, and Rob Hegele, MD
3. Hypercalcemia
   Authors: Christopher Tran, MD, and Erin Keely, MD
4. Hypercortisolism (Cushing's Syndrome)
   Author: André Lacroix, MD
5. Primary Hyperparathyroidism
   Author: Aliya Khan, MD
6. Hyponatremia
   Author: Erin Keely, MD
7. Hypoparathyroidism
   Author: Aliya Khan, MD
8. Male Hypogonadism
   Author: Stan Van Uum, MD
9. Pheochromocytoma
   Author: Jeannette Goguen MD
10. Pituitary Apoplexy
    Author: Anne Kenshole, MD
11. Pituitary Adenoma
    Authors: Karen Gomez-Hernandez, MD, and Shereen Ezzat, MD
12. Polycystic Ovary Syndrome (PCOS) in Adult Women
    Author: Sheila Laredo, MD

13. Premenopausal Osteoporosis
    Author: Aliya Khan, MD
14. Resistant/Refractory Hypertension & Primary Aldosteronism (PA)
    Author: Ally P.H. Prebtani, MD
15. Thyroid Nodule
    Authors: Muhammad Z. Shrayyef, MD, and Aliya Khan, MD
16. Thyrotoxicosis/Hyperthyroidism
    Author: Robyn Houlden, MD

QI Resource 1: Addison's Disease (Primary Adrenal Insufficiency)

Etiology/differential diagnosis

- Adrenal insufficiency may be due to adrenal destruction, dysgenesis, or impaired steroid synthesis.
- Prevalence: 100–120 per million population
- Autoimmune 80%; tuberculosis 15%; metastatic disease, HIV, hemorrhage, and genetic abnormalities 5%
- Tuberculosis remains an important cause in immigrant and Canadian First Nations populations.
- Often misdiagnosed in early stages, can mimic gastrointestinal (GI) and psychiatric disorders
- May present acutely in sepsis
- The adrenal gland has significant reserve and symptoms appear with destruction of approx 90% of the adrenal gland.
- Adrenal insufficiency may be part of an autoimmune polyglandular syndrome (APS):
  - Type 1 (APS-1): Usually occurs in children. Features include mucocutaneous candidiasis and hypoparathyroidism. Other features include hypogonadism, type I diabetes, hypothyroidism, vitiligo, alopecia, hepatitis, B12 deficiency, and malabsorption. It is associated with a mutation in the autoimmune regulatory gene (AIRE).
  - Type 2 (APS-2): Occurs primarily in adults. Components include autoimmune thyroid disease, celiac disease, gonadal failure, atrophic gastritis, and myasthenia gravis. Type 2 is often associated with autoantibodies to 21-hydroxylase and 17-hydroxylase.

History

- Symptoms—early: nonspecific: fatigue, weakness, anorexia, weight loss; advanced: hypoglycemia, orthostatic hypotension, hyponatremia, hyperkalemia, salt-craving

Physical examination

- Pigmentation (skin, mouth): hypotension with significant postural fall

Investigations

- Obtain immediate blood samples for adrenocorticotropic hormone (ACTH), cortisol, renin, electrolytes, plasma glucose before starting treatment
- Hyponatremia and hyperkalemia may not be present in the early phases of the disorder and cortisol levels may be maintained at the expense of an elevated ACTH
- If results are equivocal, use the 250 μg Cortrosyn stimulation test to determine adrenal reserve. Normal response is a 30- or 60-min postinjection cortisol over 500 nmol/L. Definitive diagnosis is crucial for management.
- Additional testing to determine the presence of antibodies to the 21-hydroxylase and the 17-hydroxylase gene may be done if there is doubt about the diagnosis.

Management

- Acute situation: hospitalize if symptomatic, draw blood for cortisol and ACTH and start IV—normal saline. Administer hydrocortisone sodium succinate 100 mg IV every 8 h, rehydrate, and gradually normalize serum sodium.
- If ACTH levels are not elevated, secondary adrenal insufficiency should be considered. A Cortrosyn stimulation test can be completed if the diagnosis is suspected.
- Hydrocortisone (cortisol) is the replacement of choice (cortisone requires conversion to cortisol, prednisone too prolonged half life to mimic diurnal secretion)
- Normal secretory rate 10–12 mg/d but usual replacement dose 15–25 mg/d in 2 or 3 divided doses (e.g., 10 mg hydrocortisone on awakening, 5 mg at noon, and 5 mg at 5pm)
- Replace aldosterone with Florinef 0.05–0.2 mg/d.
- Patient education about stress dosing and wearing of MedicAlert vital. All patients should know about emergency administration of Solu-Cortef and how and when to administer.

Monitoring:

- Use a.m. ACTH levels prior to morning cortisol dose. ACTH levels should be 2–3 times the upper limit of normal. If ACTH levels are suppressed, the patient is on too much cortisol.
- ACTH invariably elevated, 40–60 pmol/L. If >60, consider a change in regimen or increase dose
- a.m. dose should be ingested as early as possible.
- Weight gain or loss of important determinants of satisfactory control
- Monitor Florinef dosage by a.m. renin and blood pressure levels after a brief rest
- Quality of life typically suboptimal
- Increased morbidity and mortality recognized

References and Resources

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QI Resource 2: Familial Hypercholesterolemia

Etiology

- Differential diagnosis:
  - Familial defective apo B-100
  - Autosomal recessive hypercholesterolemia (ARH)
  - Sitosterolemia
  - Cholesterol 7 alpha-hydroxylase deficiency
  - Cerebrotendinous xanthomatosis
- Simon Broome criteria for diagnosis of heterozygous familial hypercholesterolemia (heFH)[1]:
  a. Cholesterol parameters
     - Total cholesterol (TC) >6.7 mmol/L mg/dL or low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L if age <16 yr
     - TC >7.5 mmol/L or LDL-C >5.0 mmol/L if age >16 yr

  b. Tendon xanthomata in first-or second-degree relative
  c. DNA-based mutation identified
  d. Family history of myocardial infarction under the age of 60 in a first-degree relative or under the age of 50 in a second-degree relative
  e. Family history of TC >7.5 mmol/L in a first-or second-degree relative or TC >6.7 mmol/L or LDL-C >4.0 mmol/L in a child or sibling under the age of 16

Definite heFH = A + B or A + C
Possible heFH = A + D or A + E
Familial hypercholesterolemia (FH) is an autosomal dominant, monogenic disorder. Prevalence of heFH is 1 in 500 (higher prevalence in founder populations, such as French Canadians); in contrast, homozygous FH (hoFH) is 1 in a million. Plasma LDL-C levels are 2–5 times higher than normal, and patients develop cardiovascular disease (CVD) in their 40s–50s. Those with hoFH have plasma LDL-C levels often exceeding 10 mmol/L and can develop CVD before the age 25. Adverse outcomes include premature CVD and sudden death.

[1]Three sets of criteria that have been used for the diagnosis of FH. The Simon Broome criteria are presented, although the USA MedPed criteria and the Dutch Lipid Clinic Network criteria could also be used. See Hovingh GK et al. Diagnosis and treatment of familial hypercholesterolemia. Eur H Journal 2013;34:962–971 for an outline of those criteria.

History

- Cardiovascular symptoms (e.g., chest pain, shortness of breath, claudication): onset, duration
- Symptoms of left ventricular outflow tract obstruction especially syncope
- Family history of premature CVD or elevated cholesterol
- History of elevated cholesterol levels at a young age
- Dietary history regarding fat and cholesterol intake and exercise duration, frequency

Physical examination

1. Visible or palpable cholesterol deposits:
   a. Arcus cornealis (whitish or bluish-gray rim along the periphery of the iris)
   b. Xanthelasma (yellowish plaque-like subcutaneous deposits on or near the eyelids)
   c. Tendon xanthomas (thickening of tendons, especially the Achilles tendon, or presence of subcutaneous nodules along the tendons—most commonly, the extensor tendons, including over knuckles, elbows and knees)
2. Systolic murmur at the base of the heart, radiating to the carotids, predominantly the right carotid, may indicate the murmur of an associated supravalvular aortic stenosis
3. Discrepancy in blood pressures between the upper extremities with the right blood pressure exceeding the left blood pressure by 20 mmHg or more
4. Diastolic decrescendo murmur of aortic regurgitation may be present.

Investigations

- Lipid panel, screen for secondary causes including hypothyroidism, nephrotic syndrome, or obstructive liver disease, and where warranted, echocardiography, exercise stress test, or equivalent.
- Baseline transaminases and creatine kinase are warranted if statin therapy is considered.
- Consider genetic testing for mutations in LDLR (LDL receptor gene), APOB (Apo B-100 gene) for familial defective apo B-100, PCSK9 (proprotein convertase subtilisin kexin subtype 9 gene), LDLRAP1 (LDLR adaptor protein 1) for (ARH), and ABCG5/ABCG8 for sitosterolemia.

Management

- Target LDL-C levels for patients with FH depend on risk categorization.
- 2012 Canadian guidelines recommend >50% reduction in LDL-C for those with a low risk factor burden and LDL-C >5.0 mmol/L; and recommend lowering LDL-C to below 2.0 mmol/L for higher-risk individuals.

- A low-fat diet is recommended, but management relies heavily on drug therapy.
- For heFH statins with other lipid-lowering agents (ezetimibe, bile-acid sequestrants) can significantly lower LDL-C and decrease CVD risk.
- Patients with hoFH benefit only modestly from even high-dose statin and other oral lipid-lowering therapy. Thus, intermittent (weekly or biweekly) LDL apheresis is required in patients to significantly reduce LDL-C levels.
- Lomitapide (an inhibitor of microsomal triglyceride transfer protein) has received limited use indications by the Health Protection Branch of Canada for the treatment of hoFH. PCSK9 inhibitors, such as evolocumab and alirocumab, have been approved for the treatment of heFH and hoFH.
- Monitoring for ischemic or valvular disease in FH is based on symptoms and relevant clinical findings.

References and Resources

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QI Resource 3: Hypercalcemia

Etiology

1. Parathyroid hormone (PTH) mediated
   - Primary hyperparathyroidism: parathyroid adenoma; parathyroid hyperplasia; parathyroid carcinoma
   - Tertiary hyperparathyroidism
   - Familial hypocalciuric hypercalcemia
   - Ectopic PTH production by tumor
2. Non-PTH mediated
   - Hypercalcemia of malignancy: parathyroid hormone related peptide mediated, osteolytic bone metastases (e.g., multiple myeloma, breast cancer)
   - Extrarenal calcitriol production: lymphoma
   - Granulomatous disease (calcitriol mediated): sarcoidosis, tuberculosis
   - Milk alkali syndrome
   - Parenteral nutrition
   - Paget's disease with immobilization
   - Endocrinopathies: hyperthyroidism, adrenal insufficiency, pheochromocytoma
   - Immobilization
3. Drugs: medications: thiazide diuretics, lithium, hypervitaminosis A, hypervitaminosis D

History

- Symptoms:
  - Can be asymptomatic if mild hypercalcemia and of gradual onset (i.e., below 3.0 mmol/L)
  - Polyuria, polydipsia
  - Renal: stones
  - Abdominal: constipation, abdominal pain, pancreatitis
  - Neuropsychiatric: cognitive dysfunction, anxiety, confusion
- Medication history (including over the counter, vitamins, calcium supplements)
- Family history for multiple endocrine neoplasia (MEN), familial hypocalciuric hypercalcemia (FHH)

Physical examination

- Blood pressure, pulse, height, weight, evidence of volume depletion, weight loss, height loss
- Evaluate for thyroid nodules; check for neck masses.
- Evidence of malignancy: lymph node examination, splenomegaly, breast examination

Investigations

- Serum calcium, albumin
  - Correct for serum albumin: increase serum calcium by 0.2 mmol/L for every 10 g/L albumin below normal
  - Ca (corrected) = calcium (measured) + (40 – albumin) × 0.02
- Ionized calcium: useful in states of albumin fluctuation and abnormal pH (e.g., infection, acutely ill)
- Serum PTH
  - Appropriately low: non-PTH mediated
  - If PTH low—serum vitamin D, TSH, free T4, SIE, chest X-ray, bone scan, ultrasound of abdomen and pelvis, mammogram if not completed recently
  - Inappropriately normal or high: PTH mediated
- Serum creatinine: renal failure
- Serum phosphate: high if 1,25-dihydroxyvitamin D mediated
- 24-h urinary calcium, creatinine, and calculate calcium-to-creatinine clearance ratio (CCCR)
  - CCCR >0.02 : PTH or parathyroid hormone related peptide mediated
  - CCCR <0.02 consider FHH
  - EKG: short QT interval

Management

- Initial management:
  - IV fluids: restore volume enabling renal calcium excretion
  - Furosemide: promote calciuresis, start after volume replete (avoid volume overload)
  - Calcitonin: limited efficacy, tachyphylaxis, provides rapid lowering of serum calcium
  - Bisphosphonates: if serum calcium above 3.0 mmol/L; zoledronate 4 mg or pamidronate 60–90 mg IV (30 mg if significant renal failure); bisphosphonates are contraindicated if eGFR <35 mL/min
  - Treat underlying cause

Also consider:

1. Glucocorticoids: for 1,25-dihydroxyvitamin D-mediated causes
2. Calcimimetics (e.g., cinacalcet): second line for PTH-mediated hypercalcemia
3. Dialysis: if refractory to above

References and Resources

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QI Resource 4: Hypercortisolism (Cushing's Syndrome)

Etiology

- Adrenocorticotrophic hormone (ACTH)-dependent
  - Pituitary corticotroph adenoma (65%)
  - Ectopic ACTH (10%)
  - Ectopic CRH (<1%)
- ACTH-independent
  - Unilateral cortisol-secreting adenoma (15%)
  - Adrenal carcinoma (5%)
  - Bilateral macronodular adrenal hyperplasia (<2%)
  - Bilateral micronodular hyperplasias (<2%)

History

- Specific symptoms of cortisol excess: onset, duration, review pictures of patient
- Facial plethora, proximal myopathy, skin thinning, easy bruising, red striae, failure of growth in children
- History of progressive cumulative manifestations: central obesity, diabetes, hypertension, hypokalemia, atherosclerotic disease
- Neuropsychological symptoms: depression, cognitive impairment, sleep disturbances
- Hirsutism, menstrual abnormalities in women; hypogonadism in men
- Osteoporosis, vertebral fractures, nephrolithiasis
- Adrenal incidentaloma, infections, thromboembolic disease
- Family history: adrenal nodules, pituitary tumors, cancers, Carney complex (myxomas, pituitary, thyroid, gonadal or other tumors), meningiomas

Physical examination

- Blood pressure, pulse, height, weight, body mass index
- Central obesity, supraclavicular fat, proximal myopathy, skin striae, skin and mucosal pigmentation, hirsutism/virilization, edema

Investigations

- Initial screening for Cushing's syndrome (CS) with either 1-mg overnight dexamethasone test, urinary free cortisol (UFC) twice, late-night salivary cortisol (LNSC) twice.
  - If abnormal (a.m. cortisol > 50 nmol/L, or UFC or LNSC above normal), repeat tests and, if consistent, refer to specialized center for diagnosis of etiology of CS.
  - Complete screening with evaluation for diabetes (fasting glucose, HbA1C), hypertension, dyslipidemia, osteoporosis, or other comorbidities.
- Etiological diagnosis of confirmed CS: fasting plasma ACTH in the morning twice.
- ACTH-independent CS: ACTH <2.2 pmol/L: computed tomography (CT) scan of abdomen without contrast to identify primary adrenal lesion (unilateral adenoma/carcinoma or bilateral hyperplasias [micro- or macronodular]).
- Intermediate ACTH: ACTH: 2.2–4.4 pmol/L: perform human corticotropin-releasing hormone (CRH) stimulation test (1 mcg/kg intravenous) to distinguish between both categories.
- ACTH-dependent: ACTH >4.4 pmol/L: pituitary magnetic resonance imaging (MRI), and confirmation tests with high-dose dexamethasone (8 mg overnight, intravenous 4 mg over 4 h), desmopressin test (10 mcg iv) or CRH test.
  - If pituitary adenoma is >6 mm and dynamic tests are compatible with Cushing's disease: send for neurosurgical resection of Cushing's disease adenoma
  - If pituitary adenoma is nonvisible, <6 mm, or discordant dynamic tests: perform inferior petrosal sinus sampling (IPSS) for ACTH and prolactin. If the central source of ACTH is present, refer to neurosurgery.

- If there is no central source of ACTH during IPSS: search for ectopic source with contrast CT scan of thorax, abdomen, octreoscan, or FDG PET scan. Surgical removal of ectopic source when possible with expected need to replace suppression of pituitary adrenal axis postop (hydrocortisone).

Management

- Therapy of Cushing's disease: selective neurosurgical removal of corticotroph tumor
  - Complete removal (60%–85% of cases): suppression of adjacent normal ACTH secreting cells will cause need for replacement with hydrocortisone with progressive recuperation over 9–15 mo.
  - Incomplete removal: partial improvement or no improvement of cortisol excess postop (5%–30%) of cases. In patients with initial remission: 10%–20% develop relapse over 10–20 yr of follow-up.
  - Monitoring for relapse: LNSC; 1-mg overnight dexamethasone test, 1 mg dex test followed by desmopressin test; UFC is the least sensitive and latest to become abnormal.
  - Consider in multidisciplinary tumor board discussion: second pituitary surgery (resectable and progressive pituitary lesion), radiotherapy (conventional or radiosurgery for incompletely resectable or invasive adenoma), medical therapy targeting ACTH secretion (cabergoline, pasireotide), steroidogenesis inhibitors (ketoconazole, metopyrone), or bilateral adrenalectomy. In the latter case, long-term monitoring for corticotroph tumor progression with pituitary MRI and ACTH levels (Nelson's syndrome) is indicated.
- Therapy of primary adrenal causes:
  - Unilateral adrenal adenoma: laparoscopic adrenalectomy with resultant secondary adrenal insufficiency (9–18 mo).
  - Adrenocortical carcinoma: open oncologic adrenalectomy when complete resection is possible with adjuvant therapy with mitotane or radiotherapy to be considered. For certain stage III cases, neoadjuvant chemotherapy (etoposide doxorubicin cisplatin) may be necessary to allow eventual surgical resection. In stage IV cases, mitotane and other steroidogenesis inhibitors plus chemotherapy.
  - Bilateral macronodular adrenal hyperplasia: search for familial cases with 1 mg overnight test and eventually for ARMC5 mutations with/without associated meningiomas. Search for aberrant hormone receptors.
  - Bilateral adrenalectomy for severe CS and BMAH: In milder forms (UFC <2× upper limit of normal, and particularly if asymmetric adrenal enlargement), unilateral adrenalectomy may provide relatively long-term correction of CS until contralateral overgrowth and recurrence.
  - Primary pigmented nodular adrenal dysplasia: search for Carney complex, familial history. Bilateral adrenalectomy for CS.
- Indications for medical therapy of CS include
  a. Acute complications of hypercortisolism, (psychosis and infection); surgery pretreatment in severe cases if surgery is delayed; hypercortisolism after unsuccessful surgery while awaiting control from radiotherapy; unresectable or metastatic tumors; and hypercortisolism due to an occult ectopic ACTH producing neuroendocrine tumor.
- Treatments include
  b. Steroidogenesis inhibitors: ketoconazole 200–1200 mg daily, metyrapone 3–5 g/d, mitotane (1–10 g daily); pituitary tumor-directed drugs (cabergoline: 1–6 mg/wk, pasireotide 300–1200 mg sc bid); a combination of drugs might be necessary to achieve eucortisolism. In patients with cyclic CS, it may be difficult to achieve stable eucortisolism, and a block and replace strategy using higher doses with replacement with hydrocortisone may be necessary.
  c. Increased risk of thromboembolism, particularly in immobilized patients and in perisurgical periods, requires adequate thromboprophylaxis with heparin or low-molecular-weight heparin. Prevention of infectious complications in immunocompromised patients should include prophylaxis with influenza, herpes zoster, and pneumococcal vaccinations.
- Long-term follow-up of patients:
  d. Replace adrenal insufficiency adequately (hydrocortisone 20–30 mg daily in 2–3 doses) with education to adjust treatment in case of stress and use of medical bracelet.
  e. Long-term therapy of comorbidities including osteoporosis, diabetes, hypertension, dyslipidemia, atherosclerosis, cognitive impairment, and depression.
  f. Patients with CS need complex investigations and long-term follow-up by an experienced multidisciplinary team to identify and correct the cause of their syndrome, monitor possible recurrence, ensure adequate hormonal replacement, and treat the psychological and multiorgan consequences of exposure to excess glucocorticoids.

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QI Resource 5: Primary Hyperparathyroidism

Etiology

- Sporadic adenoma (85%)
- Hyperplasia (15%)
- Carcinoma (<1%)
- Can be associated with familial disorders multiple endocrine neoplasia types 1, 2, 3, 4 (MEN1, MEN2, MEN3, MEN4)
- Familial isolated hyperparathyroidism
- Hyperparathyroidism jaw tumor syndrome (HPT-JT)

History

- Symptoms of hypercalcemia (onset, duration): polyuria, polydipsia, lethargy, weakness, confusion, depression, nausea, constipation, pancreatitis
- History of fragility fracture, height loss
- History of kidney stones
- History of hypertension, stroke, cardiovascular disease
- History of radioactive iodine administration
- Family history: calcium disorders, kidney disease, parathyroid disease
- Exclude other causes of hypercalcemia (granulomatous disease or occult malignancy)
- Careful review of medications including use of calcium and vitamin D supplements, hydrochlorothiazide (HCTZ), lithium use

Physical examination

- Blood pressure, pulse, height, weight
- Neck examination: palpable nodules or neck masses (are not likely parathyroid), evidence of prior neck surgery, mucosal neuromas, Marfanoid habitus
- Chest, cardiovascular examination and abdominal examination—exclude malignancy

Investigations

- Calcium (total corrected for albumin, and ionized), phosphorus, magnesium, creatinine, glomerular filtration rate (eGFR), intact parathyroid hormone, complete blood count (CBC), alkaline phosphatase
- Thyroid-stimulating hormone
- 25-Hydroxyvitamin D, 24-h urine for calcium, and creatinine
- Calcium-to-creatinine clearance ratio (CCCR) <0.02—consider inactivating mutation of the calcium sensing receptor (familial hypocalciuric hypercalcemia [FHH])
- Bone density test—include 1/3 radial site
- Ultrasound of kidneys with exclusion of occult renal stones or nephrocalcinosis

Diagnosis

- Primary hyperparathyroidism (PHPT) confirmed if calcium total (corrected for albumin) or ionized is elevated in the presence of elevated or nonsuppressed parathyroid hormone (PTH) in the absence of HCTZ or lithium use
- CCCR <0.02; consider FHH—seen in 80% of those with low ratio, 20% of FHH have higher ratio and overlap with PHPT. Falsely low CCCR—seen in vitamin D insufficiency, severe calcium, and vitamin D deficiency
- CCCR >0.02; consider PHPT
- Consider gene sequencing for calcium sensing receptor to exclude FHH in the presence of family history of hypercalcemia or if CCCR is <0.02 and persistent hypercalcemia with high normal or elevated PTH as well as presence of hypercalcemia postsurgical exploration.
- Consider hereditary forms of PHPT in those under 40
- MEN1-DNA analysis of MEN 1 gene: tumors of parathyroids, pancreas, duodenal endocrine cells, anterior pituitary
- MEN2-DNA analysis of RET protooncogene: medullary thyroid carcinoma (MTC), parathyroid, pheochromocytoma
- MEN3-DNA analysis of RET protooncogene: MTC, pheochromocytoma, parathyroid tumors, Marfanoid habitus, mucosal neuromas, diverticulosis, megacolon
- MEN4-DNA analysis of CDNK1B gene: parathyroid, pituitary, tumors of gonads, adrenals, and kidneys
- HPT-JT-DNA analysis of HRPT2 gene (parafibromin): tumors of parthyroids (often carcinomas) ossifying jaw fibromas, uterine tumors, renal tumors, pancreatic adenocarcinomas, testicular tumors, Hurthle cell thyroid adenomas
- Preoperative imaging not for diagnosis—only as a tool to guide surgical approach

Management

- Stop calcium supplements, HCTZ and review need for lithium.
- Repeat laboratory tests 3 mo after stopping HCTZ to confirm the presence of hypercalcemia.
- Exclude other causes of hypercalcemia including occult malignancy or granulomatous disease if PTH is low or mid normal.
- Correct vitamin D insufficiency and ensure 25-hydroxyvitamin D >50 nmol/L.
- Refer to experienced parathyroid surgeon (>20 parathyroidectomies annually) for imaging and surgery if there are no contraindications for surgery. Emphasize surgery especially if the following criteria are met:

  - Age <50 yr
  - Hypercalcemia calcium corrected ≥0.25 mmol/L above normal upper level
  - Osteoporosis by bone mineral density or fragility fracture
  - Nephrolithiasis
  - eGFR < 60 mL/min
- Consider medical management if patient is unwilling or unable to have surgery. Options include bisphosphonates or Cinacalcet.

References and Resources

- Bilezikian JP, Brandi ML, Eastell R, et al. 2014 Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 99(10):3561–3569.
- Khan AA, Hanley DA, Rizzoli R, et al. 2017 Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int 28(1):1–19.

QI Resource 6: Hyponatremia

Etiology

- Acute:
  - Water intoxication
  - Exercise-associated (e.g., marathons)
  - Postoperative (when given free water)
  - Drugs (e.g., Ecstasy)
- Chronic:
  - Syndrome of inappropriate hormone secretion (SIADH)—criteria: plasma osmolality <275, urinary osmolality (Uosmol) >100, euvolemic, urinary sodium (UNa) >20–30, absence of other cause including diuretics, severe hypothyroidism, hypocortisolism
  - Drug induced—selective serotonin reuptake inhibitors, diuretics, nonsteroidal anti-inflammatory drugs (NSAID)
  - Hypovolemic states—GI, renal, cutaneous loss
  - Endocrine causes—adrenal (primary or secondary) insufficiency, hypothyroidism
  - Hypervolemic states—heart failure, cirrhosis, nephrotic syndrome, renal failure
- Measure serum osmolality to rule out pseudohyponatremia (i.e., normal or elevated serum osmolality—hyperlipidemia, hyperproteinemia, mannitol, hyperglycemia)

History

- Evidence of symptoms of hyponatremia (see below)
- Water intake, drug/medication use, history of GI losses
- History of congestive heart failure (CHF), cirrhosis, renal disease

Physical examination

- Volume status, including orthostatic fall in blood pressure
- Evidence of CHF, liver disease, adrenal insufficiency
- Neurological status including loss of consciousness and confusion

Investigations

- Measure Uosmol and UNa
- Exclude secondary causes: thyroid-stimulating hormone, cortisol, Screat, Uprot, liver function tests

Management

- Based on acuity and severity based on signs and symptoms
  - Asymptomatic
  - Mild—headache, irritable, decreased concentration, depression
  - Moderate—nausea, confusion, disoriented, unstable gait/falls
  - Severe—vomiting, seizures, decreased level of consciousness, respiratory distress
- Determine volume status: hypervolemic, euvolemic, hypovolemic
- Acute (<48 h): Goal is to limit the rise in sodium to 12 mmol/L/d in acute/severe hyponatremia
  - Treat underlying cause
  - Severe symptoms: 100 mL of hypotonic 3% saline infused over 10 min. Repeat up to 3 times
  - Moderate symptoms: hypotonic 3% saline infused at 0.5–2 mL/kg/h
  - Mild/asymptomatic: fluid restriction if euvolemic/SIADH
- Chronic: Goal is to limit fluids with rise in sodium of 4–6 mmol/L/d
  - Sodium <120: consider a vasopressin receptor antagonist or vaptan (not in hypovolemic states), limited hypertonic saline followed by fluid restriction
  - Sodium >120: intervention other than treating underlying cause, volume restriction if SIADH may not be necessary

References and Resources

- Harring TR, Deal NS, Kuo DC. 2014 Disorders of sodium and water balance. Emerg Med Clin N Am 32(2):379–401.
- Verbalis JG, Goldsmith SR, Greenberg A, et al. 2013 Diagnosis, evaluation and treatment of hyponatremia: expert panel recommendations. Am J Med 126(10 Suppl 1):S1–S42.

QI Resource 7: Hypoparathyroidism

Etiology/differential diagnosis

- Postsurgical
- Radiation induced
- Metastatic disease
- Granulomatous disease
- Iron or copper deposition
- Magnesium deficiency or excess
- Genetic mutations: CASR, autoimmune regulatory gene (AIRE), parathyroid hormone (PTH), GATA3, GCMB, TBX1, TBCE, GNAS
- Pseudohypoparathyroidism (resistance state)

History

- Symptoms of hypocalcemia (onset, duration): numbness, tingling of the face, hands, feet, weakness, muscle cramping, confusion, tetany (seizures, laryngospasm, carpal spasm), bronchospasm, congestive heart failure
- History of neck surgery, radioactive iodine (RAI), radiation, cancer
- Presence of oral/vaginal candidiasis, adrenal insufficiency, hypogonadism, diabetes, hypothyroidism, vitiligo, alopecia, B12 deficiency, hepatitis
- History of RAI administration
- Hearing impairment, frequent urinary tract infection
- Cleft lip or palate surgery, cardiac surgery
- History of delayed growth, cognitive impairment
- Family history: calcium disorders, kidney disease, parathyroid disease

Physical examination

- Blood pressure, pulse, height, weight
- Chvostek's sign: tap the cheek 2 cm anterior to the ear lobe and observe for ipsilateral twitching of the upper lip
- Trousseau sign: blood pressure >systolic ×3 min and observe for carpal spasm
- Evidence of neck surgery or oral candidiasis
- Skin examination: presence of vitiligo or bronzing
- Cleft lip, cleft palate
- Albright hereditary osteodystrophy features: round face, mental retardation, short stature, obesity, brachydactyly, ectopic ossification

Investigations

- Laboratory tests:
  - Calcium, total and ionized, albumin, phosphorus, magnesium, creatinine, estimated glomerular filtration rate, intact parathyroid hormone
  - 25-Hydroxyvitamin D, 1,25-dihydroxyvitaminD, 24-h urine for calcium, and creatinine, fasting cortisol, copper, iron, TIBC, ferritin, thyroid-stimulating hormone, free T3, free T4, follicle-stimulating hormone, luteinizing hormone, estradiol, total, free testosterone, calcium-to-creatinine clearance ratio >0.33 (consider activating mutation of the calcium sensing receptor)
  - If Albright's hereditary osteodystrophy, consider pseudohypoparathyroidism and obtain further family history—maternal or paternal (pseudopseudohypoparathyroidism).
- Special investigation:
  - Consider gene sequencing for calcium sensing receptor. Prepro-PTH gene, AIRE gene (autoimmune polyendocrine syndrome type 1)—2 of 3 adrenal insufficiency, oral candidiasis, hypoparathyroidism. Other features include hypogonadism, type I diabetes, hypothyroidism, vitiligo, alopecia, hepatitis, B12 deficiency, and malabsorption.
  - GATA3 gene mutations lead to syndrome of hypoparathyroidism, deafness, and renal anomalies—consider ultrasound of kidneys.
  - Syndrome of hypoparathyroidism growth and mental retardation associated with mutations in the TBCE gene leading to short stature, cortical bone thickening, and calcification of the basal ganglia, ocular abnormalities, and hypoparathyroidism
  - DiGeorge syndrome due to mutations in the TBX1 gene results in decreases in transcription factor responsible for parathyroid gland development. Associated with abnormalities in the parathyroid and thymic gland formation, neurocognitive abnormalities, palatal, renal, ocular, and skeletal anomalies

Management

- If unstable, proceed with calcium gluconate IV 1–2 g each over 10 min, EKG monitoring followed by IV infusion of calcium gluconate 1–3 mg/kg/h.
- Calcium carbonate or calcium citrate 1–2 g TID with meals, may require up to 9 g daily, calcitriol 0.25–1.0 mcg OD to BID onset 1–2 d, offset 2–3 d or alfacalcidiol 0.5–3 mcg onset 1–2 d, offset 5–7 d.
- Normalize 25 hydroxy vitamin D
- Hydrochlorothiazide 25–100 mg/d
- PTH (1–84) start at 50 μg sc daily and decrease dose of calcitriol or alpha calcidiol by 50% gradually increase to 75 or 100 μg daily with monitoring of calcium corrected for albumin, phosphate, magnesium, creatinine

- Teriparatide 20 mcg subcutaneous twice/day (off-label) if hypocalcemia is not effectively controlled or in the presence of significant fluctuations in serum calcium[2]
- Diet low phosphate (meat, eggs, dairy, cola); consider phosphate binders if calcium phosphate product is high ; low salt diet (lowers renal calcium losses)
- Normalize magnesium
- Treatment goal: minimize symptoms
  - Calcium in the low-normal range (2.0–2.12 mmol/L or 8.0–8.5 mg/dL)
  - Minimize hypercalciuria (maintain urine calcium <10 mmol/d or 250 mg/d) and hyperphosphatemia (maintain phosphate <1.93 mmol/L)
  - Calcium phosphate product <4.4 $mmol^2/L^2$ or <55 mg^2/dL^2

References and Resources

- Bilezikian JP, Khan AA, Potts JT Jr, et al. 2011 Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 26(10):2317–2337.
- Al-Azem H, Khan AA. 2012 Hypoparathyroidism. Best Pract Res Clin Endocrinol Metab 26(4):517–522.

QI Resource 8: Male Hypogonadism

Etiology/differential diagnosis

Conditions with increased prevalence of hypogonadism (consider measuring a.m. total testosterone [TT] even if no symptoms "case finding"):

- Diabetes mellitus (±50%)
- Pituitary mass/radiation
- Medications that affect T production (e.g., opioids, 80%–90% ↓TT)
- Medications that increase metabolism (e.g., glucocorticoids)
- HIV-associated weight loss
- End-stage renal disease
- Moderate/severe chronic obstructive lung disease
- Infertility
- Osteoporosis

Additional considerations:

1. Evaluation for androgen deficiency (including laboratory tests) should not be done during (sub) acute illness.
2. Treatment in patients with classic symptoms and confirmed low TT is aimed at improving secondary sex characteristics and sexual function, subjective well-being and bone mineral density.
3. For borderline/low normal testosterone levels, there is a major lack of well-designed long-term studies on balance between beneficial effects and long-term safety.
4. Contraindications for treatment: desire for fertility, active prostate cancer, unevaluated prostate nodule/↑prostate specific antigen, severe lower urinary tract symptoms, untreated severe OSA, Hct >0.5, uncontrolled/poorly controlled heart failure.

History

- Most specific symptoms:
  - Decreased sexual development
  - Decreased libido and sexual activity
  - Decreased spontaneous erections
  - Breast discomfort, gynecomastia
  - Decreased axillary/pubic hair, reduced shaving
  - Very small/shrinking testes
  - Infertility
  - Osteoporosis
  - Hot flashes
- Less specific symptoms
  - Decreased energy/motivation/initiative
  - Feeling sad/blue, depressed
  - Poor concentration and memory
  - Sleep disturbance
  - Mild anemia
  - Reduced muscle bulk and strength
  - Increased body fat, body mass index (BMI)
  - Diminished physical or work performance

Regarding erectile dysfunction (particularly if nontestosterone related): this indicates ↑risk for cardiovascular events: discuss with patient, assess additional risk factors + consider treatment (effect of testosterone [T] treatment on cardiovascular risk is controversial!)

Physical examination

- Weight
- BMI
- Blood pressure
- Decreased muscle mass
- Deficient androgenisation
- Gynecomastia
- Testicular examination

Investigations

- TT × 2, obtained in early a.m. (8–10 a.m.)
- Additional tests luteinizing hormone, follicle-stimulating hormone (prolactin), looking for central deficit, for which most common causes are hyperprolactinemia, pituitary tumors, and opioids

[2]The Food and Drug Administration in the US has approved PTH (1–84) in the United States for the control of hypocalcemia in hypoparathyroidism. This has not yet been approved in Canada by the Health Protection Branch, Health Canada.

- Sex hormone binding globulin (SHBG) if possibly altered (see below)
- Lipid profile, glucose, HbA1c, CBC, prostate specific antigen (baseline before treatment)

Free and bioavailable testosterones are theoretically better, but assay reliability is a significant issue, so these are not recommended for general use (may be useful with borderline TT results).

SHBG is altered:
Increased: aging, hepatic cirrhosis and hepatitis, hyperthyroidism, anticonvulsants, estrogens, HIV
Decreased: moderate obesity, nephrotic syndrome, hypothyroidism, glucocorticoids, acromegaly

Management

Comparison testosterone treatment options:

Modality	Injection	Transdermal	Oral
Frequency	1–4 wk	Daily	2–3 times daily
Specific issue	Potential fluctuating TT ("roller coaster")	Patch—25%–30% skin irritation Contamination, issue of sweating	Requires intake with fatty food
Monitoring TT, Hct (target <0.54) Q 3 mo → annually	Halfway between injections	Any time	3–5 h after intake (more challenging)
Compliance	Well monitored	Subjective	Subjective/absorption

In case of nonresponse to treatment, consider: compliance issue, malabsorption, insufficient dose, unsatisfactory formulation; symptoms are not caused by low testosterone. Persistent erectile dysfunction: consider T treatment plus PDE_5 inhibitor.

References and Resources

- Bhasin B, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force Endocrine Society. 2010 Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 95(6):2536–2559.
- Oskui PM, French WJ, Herring MJ, et al. 2013 Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. J Am Heart Assoc 2(6):e000272. doi: 10.1161/JAHA.113.000272.
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QI Resource 9: Pheochromocytoma

Etiology/differential diagnosis

- Normally benign neuroendocrine tumor of the adrenal medulla or extra-adrenal chromaffin tissue
- Other causes of labile and paroxysmal hypertension, sweating, arrhythmias

History

- Hypertension, suggestive of a secondary cause (e.g., onset <30 yr old or >50 yr old); paroxysmal or severe (>180/110), especially if not controlled by three antihypertensive agents
- Presence of the classic triad (3 P's): headache (pain), palpitation, and perspiration associated with hypertension
- May be precipitated by anesthesia, monoamine oxidase inhibitors, beta-blocker, micturition, change in abdominal pressure
- Hypertensive crisis, including symptoms of cardiovascular disease (cardiovascular accident, angina, congestive heart failure, cardiovascular shock)
- Less common presentations: pallor, flushing, weight loss, new onset diabetes mellitus, cardiomyopathy
- Personal history or family history of multiple endocrine neoplasia (MEN) type 2 or 3, Von Hippel-Lindau (vHL), neurofibromatosis type 1 (NF-1), familial paraganglioma syndromes (e.g., genetic succinate dehydrogenase deficiency syndromes [SDHB/D], etc), or any clinical manifestations of these syndromes
- Adrenal incidentaloma

Physical examination

- Hypertension (can be intermittent), weight loss, postural drop in blood pressure
- Stigmata of hypertensive complications: hypertensive retinopathy, signs of cardiac hypertrophy (sustained apex, S4) or congestive heart failure, elevated JVP, enlarged, displaced apex, S3, peripheral edema)
- Stigmata of underlying genetic syndrome: MEN2 (thyroid mass), MEN3 (thyroid mass, Marfanoid habitus, mucosal neuromas), vHL (retina hemangioma, neurological symptoms associated with cerebellar and/or spinal hemangioblastoma), NF-1 (café au lait skin lesions, neurofibromas).

Investigations

Laboratory tests:
- 24-h urine for fractionated metanephrines and catecholamines, and creatinine (to ensure complete collection)

- Plasma metanephrines have higher specificity and can be measured if urine metanephrines are only modestly elevated (for sporadic pheochromocytoma, negative test excludes disease)

Note:

- *Beware of false-positive and false-negatives (all the tests have some overlap between normal and disease-states), especially for values less than 2-fold elevated above the cut-point (and less than 4-fold elevated about the cut-point for plasma metanephrines).*
- *For those modestly elevated values, consider the possibility of a false-positive result when*
  - *the result is not elevated on repeat testing;*
  - *the patient has a low pretest probability;*
  - *test may have not been done properly (e.g., you identify possible contaminating substances, a suboptimal assay, or the patient was not prepped properly for plasma testing);*
  - *the patient has untreated sleep apnea; or*
  - *the imaging is not typical for a pheochromocytoma.*
- *If you suspect false-positive result:*
  - *make sure the testing was done properly;*
  - *repeat labs, especially during symptoms and follow-up over time;*
  - *for borderline urine metanephrines, check plasma metanephrine levels;*
  - *for borderline plasma metanephrines, consider clonidine suppression test of plasma normetanephrine, if available;*
  - *rule out sleep apnea.*
- *If high pretest probability (e.g., working up a suspicious adrenal mass), may need to proceed as if it is a pheochromocytoma).*

Imaging:

- After diagnosis is confirmed biochemically, the tumor is localized by imaging the abdomen either with computed tomography (sensitivity 95%, specificity 70%) or magnetic resonance imaging (sensitivity 99%, specificity >70%). Pheochromocytoma may look different from adrenal cortical tumor (latter more likely to be small, homogeneous, low Hounsfield units [HU, <10], rapid washout of contrast (>50% in 10 min).
- Meta-iodo-benzyl-guanidine (MIBG) scanning can be used to
  - detect tumors outside the adrenal glands (paragangliomas) if they are not picked up on other imaging;
  - confirm if the mass is a pheochromocytoma, if imaging and history is not convincing; and
  - stage for metastatic disease if the tumor is large, extra-adrenal, or associated with SDHB mutation.

MIBG-I^{131} has a sensitivity of 80%, specificity of 95% for neuroendocrine tumors.

Management

Treatment goals:

- Laparoscopic surgical resection by experienced surgeon and anesthesiologist.
- Preoperative preparation is usually achieved with phenoxybenzamine (a noncompetitive alpha-blocker) for the 2 wk before surgery, with salt supplementation and the addition of a beta-blocker when required, for tachycardia. The literature does describe successful surgery with other antihypertensive agents (there are no definitive trials).
- Postoperative management is usually in an intensive care unit setting, watching for blood pressure control (both high and low) and hypoglycemia.

Long-term management:

- Annual monitoring for recurrence, with clinical examination and 24-h urine for fractionated catecholamines, metanephrines, and creatinine.
- First-degree family members need biochemical screening.
- Consider genetic testing (most frequent mutation is vHL) as genetic disorder is found in up to 30% of cases. Pattern of disease presentation (age of patient, locale of tumor, bilateral, epinephrine vs norepinephrine production, other manifestations) can help guide which gene to test for. Consider genetic testing in patients with
  - paraganglioma;
  - bilateral adrenal pheochromocytoma;
  - unilateral adrenal pheochromocytoma and a family history of pheochromocytoma;
  - unilateral adrenal pheochromocytoma at a young age (e.g., <45 yr); or
  - clinical findings suggestive syndromic disorder.

Patients found to have a genetic cause will need regular screening for other manifestations of the underlying disorder.

References and Resources

- Eisenhofer G, Pacak K, Maher ER, et al. 2013 Pheochromocytoma. Clin Chem 59(3):466–472.
- Därr R, Lenders JW, Hofbauer LC, et al. 2012 Pheochromocytoma—update on disease management. Ther Adv Endocrinol Metab 3(1):11–26.
- Lenders JW, Eisenhofer G, Mannelli M, Pacak K. 2005 Pheochromocytoma. Lancet 366(9846):665–675.
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QI Resource 10: Pituitary Apoplexy

Etiology/differential diagnosis

- Previously unrecognized macroadenoma (90%)
- Known nonfunctioning or prolactinoma (infarct rate 2%–12%)
- Major surgery, especially cardiac
- Prior pituitary irradiation
- Anticoagulation/coagulopathy
- Major head trauma
- Dynamic pituitary testing
- Pregnancy and the puerperium
- Subarachnoid hemorrhage, meningitis

History

- Sudden severe headache (95%), visual disturbance: field defects (70%) ophthalmoplegia (40%).
- Varying levels of impaired consciousness and signs of adrenal insufficiency, nausea, vomiting, and hypotension.
- Neck stiffness
- History of head trauma or pregnancy or pituitary irradiation or endocrine stimulation tests
- Bromocriptine therapy

Physical examination

- Blood pressure, pulse, neurological examination evaluating level of consciousness, motor, sensory function, visual fields (classically bitemporal superior quadrant defect), assess extra ocular muscle

Investigations

- Obtain cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, prolactin, and electrolytes.
- Computed tomography of the head as soon as possible (best imaging choice within 4 d of presentation. Magnetic resonance imaging preferable for subacute presentation).

Management

- If diagnosis suspected, admit to intensive care unit, start first dose dexamethasone 4 mg bid or IV hydrocortisone every 6 h for glucocorticoid support and cerebral edema control.
- Indications for neurosurgery consultation for transsphenoidal decompression: bitemporal hemianopsia; raised intracranial pressure: ophthalmoplegia (surgery less frequently recommended than in the past).

Prognosis:

- Ophthalmoplegia generally improves, visual defects persist
- Permanent glucocorticoid replacement needed in 70%–80%, thyroxin replacement in 60%, sex hormone replacement in 60%, may benefit from GH replacement; ongoing surveillance for tumor regrowth important

Partial pituitary insufficiency:

- Detectable in 50% after moderate/severe traumatic brain injury
- Consider in all cases of hypogonadism
- Failure of lactation and resumption of menses following delivery

References and Resources

- Möller-Goede DL, Brändle M, Landau K, et al. 2011 Pituitary apoplexy: re-evaluation of risk factors for bleeding into pituitary adenomas and impact on outcome. Eur J Endocrinol 164(1):37–43.
- Ranabir S, Baruah M. 2011 Pituitary apoplexy. Indian J Endocrinol Metab 5(7):188–S196.
- Briet C, Salenave S, Benneville J-F, Laws ER, Chanson P. 2015 Pituitary apoplexy et al. Endocr Rev 36(6):622–645.

QI Resource 11: Pituitary Adenoma

Clinical classification

- By mode of presentation:
  - Incidentally discovered (incidentaloma)
  - Discovered due to clinical manifestations suggestive of pituitary dysfunction or compression of structures in close proximity to the sella turcica
  - Not all pituitary lesions are adenomas. Consider other diagnoses including hyperplasia, craniopharyngiomas, Rathke's cleft cyst, hypophysitis, metastases, and other sellar lesions.
- By functional status:
  - Clinically functioning (most frequently lactotroph adenomas followed by somatotroph adenomas, corticotroph adenomas, and others)
  - Clinically nonfunctioning (most frequently gonadotroph adenomas)
- By size:
  - Microadenomas (<1 cm)
  - Macroadenomas (≥1 cm)
- By genetic etiology:
  - Sporadic: non syndromic and McCune-Albright syndrome
  - Associated with familial disorders: multiple endocrine neoplasia types 1 and 4 (MEN1, MEN4), familial isolated pituitary adenoma (FIPA), Carney complex, familial paragangliomas types 1, 4, and 5

History

- Symptoms of compression: visual field deficits and blindness
- History of headaches
- Symptoms of hypopituitarism: fatigue, reduced appetite, weight loss, nausea, malaise, cold intolerance, abdominal pain, amenorrhea, infertility, reduced libido, reduced exercise capacity, loss of body hair, shrinking testes
- Symptoms of hormonal excess: prolactin (amenorrhea, galactorrhea, infertility, decreased libido, gynecomastia), growth hormone/IGF-1 (increase in shoe and ring size, coarsened facial features, soft-tissue swelling, joint pain, hyperhidrosis, sleep apnea, deepening of the voice), corticotropin/cortisol (hyperpigmented wide striae, proximal muscle weakness, easy bruising, progressive predominantly central weight gain, menstrual disturbances), thyrotropin/thyroid hormones (palpitations, heat intolerance, tremor)
- History of hypertension, diabetes or low bone mass in young individuals
- History of hypercalcemia, lung/thymic/pancreatic/gastric/duodenal neuroendocrine tumors, paragangliomas
- Family history: pituitary tumors, parathyroid tumors, lung/thymic/pancreatic/gastric/duodenal neuroendocrine tumors, pheochromocytomas/paragangliomas

Physical examination

- Blood pressure, pulse, height, weight
- Visual field examination on confrontation
- Identification of features suggestive of
  - acromegaly (frontal bossing, coarsened facial features, prognathism, teeth separation, macroglossia, soft-tissue swelling, thick skin, Tinel's sign and Phalen's test for carpal tunnel syndrome)
  - Cushing's disease (rounded plethoric face, hirsutism, acne, retrocervical and supraclavicular fat pad, skin atrophy, ecchymoses, wide and pigmented striae, proximal muscle weakness, central obesity)
  - hyperthyroidism (diffuse goiter, tachycardia, tremor, hyperreflexia)
  - McCune Albright syndrome (asymmetric growth of the face, uneven growth of leg bones, scoliosis, café au lait skin spots)
  - Carney complex (skin myxomas, pigmented lentigines, blue nevi)
  - hypogonadism (testes <5 mL, gynecomastia, reduced body hair)

Investigations

- In patients with incidentalomas, screen for pituitary hypofunction and hyperfunction:
  - Basal morning pituitary function tests for patients with macroadenomas and those with microadenomas who have symptoms suggestive of hypopituitarism: adrenocorticotrophic hormone, cortisol; insulin-like growth factor 1 (somatomedin C, IGF-1); thyroid-stimulating hormone (TSH), free thyroxine (FT4); follicle-stimulating hormone, luteinizing hormone, estradiol in women and total testosterone in men; prolactin
  - Prolactin for all patients
  - Consider screening for GH excess by measuring an IGF-1.
  - Screen for Cushing's syndrome if clinically suspected (1-mg overnight dexamethasone suppression test for plasma cortisol or 2 measurements of either free urine cortisol or late-night salivary cortisol)
  - Screen for hyperthyroidism if clinically suspected (TSH, free T4, Free T3)
- In patients who present with a clinical syndrome suggestive of anterior pituitary hyperfunction biochemical testing should be tailored accordingly and include basal morning pituitary function tests when concomitant hypopituitarism is suspected (macroadenomas or presence of symptoms)
- Formal visual field testing in patients with a tumor that abuts or compresses the optic chiasm
- Magnetic resonance imaging of the sella, if possible, for patients in whom the diagnosis of a pituitary tumor was made based on a computed tomography scan or clinically suspected
- Screen for primary hyperparathyroidism in patients with a family history of MEN1/MEN4 or who are ≤40 yr old
- Consider genetic testing for aryl hydrocarbon receptor interacting protein (*AIP)* germline mutations in patients in whom FIPA is suspected: GH producing pituitary macroadenoma diagnosed before age 30 yr, microadenomas (except microprolactinomas) diagnosed before age 18 yr, gigantism, family history of pituitary adenoma in a first-degree relative
- In the absence of a positive family history, if there are associated clinical features suggestive of a syndrome, then genetic testing should be directed toward identifying that specific defect:
  - MEN1 screen for *MEN1* mutations; MEN4 consider screening for *CDKN1B* mutations in patients who have already tested negative for *MEN1* mutations, Carney complex, screen for *PRKAR1A* mutation
- Genetic testing for *SDHx* mutations in patients with previous history of paraganglioma

Differential diagnosis

- Consider an etiology distinct from pituitary adenoma in patients with diabetes insipidus (DI). In such cases, review of imaging studies with a radiologist may be helpful,
- Consider the possibility of a pituitary metastasis in individuals with metastatic carcinoma, particularly if they have a history of DI.
- Consider the possibility of a Rathke's cleft cyst in patients with purely cystic lesions and mild hyperprolactinemia.

Management

- Medical therapy:
  - Cabergoline (more effective), quinagolide, or bromocriptine for patients with macroprolactinomas or symptomatic microprolactinomas
  - Dopamine agonist or oral contraceptive for women with microprolactinomas who do not desire pregnancy
  - Consider somatostatin analogue therapy as a first option in acromegalic patients with tumors that cannot be completely resected
  - Consider medical management of Cushing's disease if trans-sphenoidal resection is not possible. Options include pasireotide, ketoconazole (off-label), and cabergoline (off-label).
- Refer to experienced pituitary surgeon in the setting of
  - Macroadenomas (other than prolactinomas) causing visual abnormalities or other neurological compromise
  - Functional tumors (except prolactinomas)
  - Prolactinoma not responding to optimal dopamine agonist therapy and causing visual abnormalities
- Consider referring to experienced pituitary surgeon in the setting of:
  - Growing tumor causing progressive loss of pituitary function, approximating the optic chiasm, or invasion of other intracranial structures.
  - Loss of pituitary function
  - Macroadenoma with extrasellar extension in a woman desiring to conceive
  - Prolactinoma not responding to optimal dopamine agonist therapy and causing hypogonadism
- Treatment goals:
  - For patients with pituitary adenomas and visual defects or hypopituitarism, the goal is to restore vision and/or pituitary function.
  - For patients with functional syndromes, the goal is to abolish hormonal excess and associated comorbidities.

References and Resources

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QI Resource 12: Polycystic Ovary Syndrome (PCOS) in Adult Women

Etiology/differential diagnosis

PCOS is due to a combination of genetic and environmental factors. Guidelines currently available include the NIH Guidelines, the Rotterdam Criteria and the Androgen Excess and PCOS Society criteria. The Rotterdam Criteria are currently most commonly used, are endorsed by the Endocrine Society and require woman to meet at least 2 out of 3 criteria. Other causes compatible with symptoms must be excluded:

1. Oligo or anovulation
2. Hyperandrogenism (clinical or biochemical or both)
3. Polycystic ovaries on ultrasound

Other causes that should be excluded:

- Pregnancy (beta-human chorionic gonadotropin)
- Premature ovarian insufficiency (follicle-stimulating hormone [FSH] – often done on day 3 as an assessment of ovarian reserve)
- Functional hypothalamic amenorrhea (luteinizing hormone, FSH, estradiol)
- Hyperprolactinemia
- Thyroid-stimulating hormone

Note: thyroid disease typically causes changes in menstrual flow rather than regularity

- Adrenal tumor (watch for dehydroepiandrosterone sulfate [DHEAS] level more than 3 times the upper limit of normal)
- Ovarian tumor (watch for total testosterone more than 5 times the upper limit of normal)
- Cushing's syndrome ruled out clinically. Only do hormonal testing if symptoms or signs are concerning for cortisol excess, as yield is low and screening can result in false positives
- Nonclassic congenital adrenal hyperplasia (follicular phase 17-hydroxyprogesterone; most commonly done on day 3 to align with FSH testing)

History

- Menstrual history: menarche and onset of menstrual irregularity
- Oligo or amenorrhea: periods less frequent than every 35 d on average and unpredictable; some studies use less than 8–10 periods per year
- Fertility concerns, previous obstetrical history
- History of dysfunctional uterine bleeding suggesting risk for endometrial hyperplasia/cancer
- Hyperandrogenism: clinical or biochemical evidence of androgen effect
  - Elevation in any one traditional androgen measure (total, free/bioavailable testosterone, DHEAS or evidence of hirsutism on the basis of the Ferriman-Gallwey score)
  - Androgenetic alopecia and adult acne are also evidence of hyperandrogenism but harder to quantitate
- Presence of polycystic ovaries on previous ultrasound examinations as well as endometrial assessment
- Assessment of metabolic risk: Type 2 diabetes mellitus, hypertension, dyslipidemia
- Assessment of other related issues: sleep apnea, fatty liver, mood disorders
  (exclude other causes—e.g., galactorrhea for high prolactin (PRL), rapid evolution of symptoms for tumor, etc.)
- Determine patient's primary concern as PCOS is complex and all patient concerns need to be evaluated and addressed

Physical examination

- Height, weight, waist circumference, body mass index (BMI), blood pressure
- Skin examination for acanthosis nigricans, skin tags: nape of neck, groin, axillae, underneath and between breasts are common areas
- Hirsutism based on Ferriman-Gallwey score

Note: For women of East Asian ethnicity, any hair on abdomen is considered abnormal.

- Adult acne: face including forehead, cheeks, chin
- Androgenetic alopecia: thinning hair, increased visibility of scalp in frontal, temporal or crown areas of scalp with relative sparing of hair in occipital area
- Virilization features: change of voice, clitoromegaly, increased musculature, loss of breast tissue and other female pattern adiposity

Note: Virilization is not a feature of PCOS and must exclude adrenal/ovarian tumors and occasionally congenital adrenal hyperplasia

- May have dorsal and supraclavicular fat pads but will not have the distal atrophy/weakness/thin skin/easy bruising/large striae typical of Cushing's syndrome

Investigations

A 75-g 2-h glucose tolerance test is recommended, particularly if BMI ≥ 25 kg/m^2 due to higher risk of prediabetes and diabetes than the general population

- Fasting plasma glucose and HbA1c underdiagnose prediabetes and diabetes
- Lipid and metabolic profile should be repeated every 3–5 yr; earlier in presence of prediabetes

Management

- Individualize management based on symptoms and concerns (cosmetic, fertility issues, or vascular risk)
- Oral contraceptive pill (OCP) are first-line for menstrual irregularities and hyperandrogenic symptoms
- Advise regarding risks and benefits of OCP (venous thromboembolic and cardiovascular disease)
- If risks outweigh benefits: regular progesterone withdrawal may be used to manage menstrual abnormalities (but will not have beneficial effects on hyperandrogenism)
- Consider additional antiandrogen treatment for hyperandrogenic women with and without OCP Do not use without adequate contraception if sexually active with male partners
- Metformin is of limited effectiveness for hyperandrogenic symptoms and for fertility, may regulate cycles if cannot use/decline hormonal treatment. Metformin is considered for prediabetes or diabetes in women with PCOS
- Clomiphene citrate is first line for infertility, does increase risk of twins, and higher order multiples.[3] If fail to conceive with clomiphene citrate, refer to a reproductive endocrinology/infertility specialist for advanced reproductive technologies
- Practice regarding use of letrozole is mixed at this time. If prescribing letrozole, patients should be advised about the potential and uncertain risks for fetal malformation.[1]

References and Resources

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[3]Practice is mixed vis-à-vis choice of prescribing of letrozole vs clomiphene. A large randomized controlled trial demonstrated that letrozole appears to have superior live birth rates compared with clomiphene citrate (see Legro, R.S., Brzyski, R.G., Diamond, M.P. et. al. (2014). Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *New England Journal of Medicine*, 371(2), 119–129)). There is uncertainty in the literature regarding whether letrozole may increase the risk of malformation in the fetus.

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QI Resource 13: Premenopausal Osteoporosis

Causes of low bone mineral density (BMD) and skeletal Fragility in premenopausal women

- Hypogonadism (primary and secondary)
- Primary hyperparathyroidism
- Thyrotoxicosis
- Hypercortisolism
- Growth hormone deficiency
- Osteomalacia
- Myeloproliferative disorders
- Connective tissue disorders
- Malabsorptive states (e.g., celiac disease)
- Hepatic disorders (e.g., primary biliary cirrhosis)
- Inflammatory bowel disease
- Renal disease
- Hypercalciuria
- Osteogenesis imperfecta
- Neurological disorders (spinal cord injury, cerebral palsy, long-term immobilization, Duchenne muscular dystrophy)
- Systemic lupus erythematosis
- Hypophosphatasia
- Idiopathic
- Medications:
  - Prednisone
  - Anticonvulsants (e.g., phenytoin, phenobarbital)
  - Heparin (long-term)
  - Lithium
  - Cytotoxic chemotherapy
  - Gonadotropin-releasing hormone agonists
  - Depot medroxyprogesterone acetate

History

- Fracture history from birth till presentation (traumatic vs fragility)
- Age at menarche, menstrual history (periods of prolonged amenorrhea)
- Pregnancy history, infertility, duration of breast feeding for each child
- Joint laxity, dental problems, easy bruisability, hearing impairment (findings suggestive of osteogenesis imperfecta)
- Metatarsal fractures, early dental loss (suggestive of hyophosphatasia)
- Delayed growth in childhood and adolescence
- History of renal stones
- Smoking, alcohol history, dietary calcium intake
- History of eating disorders (bulimia, anorexia)
- Contraceptive history (use of depoprovera, age of initiation, and duration)
- Family history of osteoporosis, fragility fracture, calcium disorders, kidney disease, parathyroid disease

Physical examination

- Blood pressure, pulse, height, weight
- Assess for features of osteogenesis imperfecta (dentition, bluish sclerae, easy bruisability or joint laxity)
- Thyroid examination
- Features of hypercortisolism
- Tanner staging
- Cardiovascular examination
- Evaluate for features of Turner's syndrome
- Marfanoid habitus (Marfan's syndrome) or features of Ehlers-Danlos syndrome with joint laxity
- Spinal tenderness
- Kyphosis
- Iliocostal distance
- Wall-occiput distance

Differential diagnosis

- Osteoporosis confirmed in the presence of fragility fractures and not solely on the basis of low BMD in premenopausal women or men under the age of 50 yr
- Fragility fracture of vertebrae confirms presence of osteoporosis. Two or more long bone fractures by age 10 or 3 or more long bone fractures by age 19 and a BMD *Z*-score of ≤–2.0 confirms the presence of osteoporosis
- BMD evaluated at lumbar spine, total hip, femoral neck and in children. Total body less head "lower than expected for age" if *Z*-score ≤ –2.0
- BMD is normal if within 2 standard deviations of age matched reference range (*Z*-score >–2.0)
- Consider evaluation of bone age in children with delayed growth and/or pubertal development
- Consider DNA analysis for the COL 1A1 and 1A2 genes if clinical features of osteogenesis imperfecta are present or tissue nonspecific alkaline phosphatase if suspect hypophosphatasia.
- Consider bone biopsy if fragility fractures are present and cause not identified.

Investigations

- Laboratory investigations: Serum calcium (corrected for albumin), CBC, phosphate, magnesium, liver function tests, thyroid-stimulating hormone, creatinine, alkaline phosphatase, FSH, estradiol (females), total and free testosterone (males), luteinizing hormone, prolactin

IgF-1, 24-h urine collection for calcium and creatinine, 25-hydroxy vitamin D, parathyroid hormone

- Additional investigations: Celiac profile, 24-h urine for free cortisol

Management

- Review use of medications associated with bone loss.
- Normalize BMI (20–25), correct hypogonadism.
- Correct underlying cause for osteoporosis if identified.
- Ensure adequate intake of calcium and vitamin D.
- Correct vitamin D insufficiency and maintain 25OH vitamin D 75–120 nmol/L.
- Smoke cessation, limit alcohol and coffee consumption, initiate weight bearing exercise program, switch to estrogen containing oral contraceptives if depoprovera prescribed
- Consider bisphosphonate therapy in the presence of glucocorticoid therapy or osteogenesis imperfecta in the presence of fragility fracture, or evidence of increased bone resorption on bone biopsy.
- Consider anabolic therapy in the presence of impaired bone formation on bone biopsy.

References and Resources

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QI Resource 14: Resistant/Refractory Hypertension & Primary Aldosteronism (PA)

Definition, etiology, and screening

Definition of resistant/refractory hypertension

- Blood pressure (BP) ≥ 140/90
- Medication adherent
- Full doses of 3 antihypertensives including thiazide or thiazide like diuretic (along with standard first line Tx: ACEI/ARBs, dihydropyridine (DHP) CCBs based on Hypertension Canada recommendations and compelling indications) and BP still not controlled (>140/90)
- BP controlled with 4 or more antihypertensive agents
- r/o Pseudoresistance (poor/inaccurate bp measuring technique and white-coat effect)

When to consider secondary hypertension:

- Extremes of age: 20 or > 50 yr old
- Abrupt worsening
- Severe >180/110 mmHg
- Refractory to ≥3 drugs (one of them a thiazide or thiazide like diuretic)
- End organ damage out of proportion to hypertension (HTN)
- Clues to secondary hypertension: clinical; biochemical (e.g., hypokalemia); imaging (e.g., adrenal incidentaloma)
- Absence of family history of essential hypertension
- Family history of secondary hypertension

Causes of secondary hypertension (<5%–10% of all causes of hypertension)

- Endocrine: Cushing's syndrome, mineralocorticoid excess: for example, PA, pheochromocytoma, acromegaly (see other modules for more details on other causes of endocrine hypertension)
- Renal: chronic parenchymal renal disease, renal artery stenosis
- Cardiac: coarctation of the aorta
- OSA
- Drugs/toxins: alcohol, cocaine, OCPs, corticosteroids, preparations to certain natural licorice, NSAIDs, OTCs, TKIs, Erythropoetin, certain herbal products (e.g., Ma huang [ephedra])
- Pregnancy related: Pre-eclampsia (>20-wk GA); Gestation induced HTN

When to screen for PA:

- Uncontrolled hypertension (>140/90) despite use of 3 drugs, including a thiazide or thiazide-like diuretic
- Hypertension requiring 4 or more drugs for adequate control <140/90
- Hypertension with easily provoked thiazide-induced hypokalemia
- Spontaneous hypokalemia with hypertension
- Hypertension with known adrenal mass
- Hypertension with a family history of PA

History

- Duration, severity, and progression of HTN
- Home and/or 24-h ambulatory blood pressure readings
- Complications/End organ damage (cardiovascular disease, congestive heart failure, atrial fibrillation, stoke, renal, retinal)
- Assess adherence to antihypertensive therapy (doses, regimen, timing); check with pharmacy
- Ask about drugs/toxins (NSAIDs, herbals, sympathomimetics, licorice, corticosteroids, alcohol, OCPs, Epo)
- Assess sodium intake/dietary history
- Obesity, diabetes, dyslipidemia, smoking
- Family history of hypertension
- Pregnancy, last menstrual period
- Assess for clues re: secondary HTN

Physical examination

- BP (both arms, supine and standing, legs, ABIs prn), pulse, height, weight, BMI
- Look for end organ damage (CVS, pulses, bruits, retina)
- Features of secondary HTN (e.g., Cushing's syndrome, acromegaly, renal bruits)

Investigations

- Electrolytes (potassium), creatinine, urinalysis, fasting blood glucose, HbA1c, fasting lipids, TSH
- Electrocardiogram (ECG)
- 24-h ambulatory blood pressure monitoring
- 24-h Na/Creat
- Echo if indicated
- If indicated → tests for secondary HTN (biochemical, imaging, nuclear medicine, sleep study)

PA screening algorithm:

- Measure a.m. plasma aldosterone (pmol/L) and renin/ renin activity once hypokalemia corrected in a.m. after patient ambulatory.
- Agents that markedly affect the results of testing (aldosterone antagonists, potassium sparing and wasting diuretics) should be withdrawn at least 4 wk prior
- If a normal or negative" aldosterone-to-renin ratio (ARR), testing should be repeated again after angiotensin-converting enzyme inhibitors, angiotensin- are held maximize the sensitivity of the test; use of alpha-blockers, hydralazine, or long-acting nondihydropyridine calcium channel blockers (verapamil/diltiazem) may be necessary for blood pressure control in the interim.
- Note, beta-blockers and centrally acting α2 agonists can give false positive ARR.
- If the patient is a woman using an oral contraceptive, high false positive rates may result when using direct renin concentration measures. If possible, the OCP should be discontinued for 1 mo prior to the test or alternately, the ARR should be determined using a plasma renin activity

Interpretation of the ARR[a]

Renin Method and Units	Weak Positive Result	Strong Positive Result
Plasma renin activity (ng/mL/h)	ARR 550–750	ARR > 750
Renin concentration (mU/L)	ARR 60–90	ARR > 90
Renin concentration (ng/L)	ARR 100–144	ARR > 144

[a]Interpretation of ARR is dependent upon the local laboratory method for renin measurement but assumes standard reporting of aldosterone in pmol/L.

Confirmatory testing PA

*interfering drugs should continue to be held if required/ possible as outlined above

a. Saline loading tests (perform either):
   i. Administer 2 L of normal saline intravenously over 4 h with the patient in a recumbent position. Primary aldosteronism is defined as a postinfusion plasma aldosterone > 280 pmol/L. If < 140 pmol/L, primary aldosteronism is unlikely. Values in between are considered indeterminate. This test is considered contraindicated in the presence of severe, uncontrolled hypertension, renal impairment or known left ventricular dysfunction.
   ii. Administer oral sodium chloride, 200 mmol/d (50 mEq/1 tsp tid) for 3 d, with primary aldosteronism defined as a 24-h urinary aldosterone >33 nmol/d (measured from the morning of day 3 to the morning of day 4). If <28 nmol/d, primary aldosteronism is unlikely. For appropriate interpretation, 24-h urine sodium should exceed 200 mmol/d
b. A strongly positive ARR, spontaneous hypokalemia, and undetectable renin, with a plasma aldosterone >550 pmol/L.
c. Captopril suppression test: Administer 25–50 mg captopril orally after the patient has been sitting or standing for 1 h. While seated, renin and plasma aldosterone levels should be measured at time zero and 1–2 h after ingestion. 1° aldosteronism is unlikely if plasma aldosterone is suppressed by >30% following captopril ingestion. In primary aldosteronism, plasma aldosterone remains elevated, whereas renin remains suppressed.

Subtype classification PA

a. CT scanning (or MRI) can help localize the presence of adrenal lesion(s), however, in patients older than 35, the specificity of anatomical imaging may be poor. If imaging demonstrates an adrenal lesion/adenoma, it may be nonfunctional. Therefore, if surgery to remove a suspected unilateral source of primary aldosteronism is planned, selective adrenal venous sampling (AVS) should be considered first (to verify that abnormally appearing adrenal gland is the source of hypersecretion).
b. AVS may not be necessary if a definite adrenal lesion > 1 cm and
   - < 35 yr old, moderate-severe HTN, hypokalemia, very high ARR, aldolsterone > 685 pM
c. AVS should be conducted in centers with experience in performing this diagnostic technique.
d. Selective genetic testing for glucocorticoid remediable aldosteronism in patients with confirmed 1° aldosteronism and either
   i. A family history of primary aldosteronism or stroke at young age (≤40 yr old); or
   ii. Onset of hypertension ≤20 yr old and negative adrenal imaging and/or bilateral aldosterone excess on adrenal vein sampling.

Management

- Adherence
  - Combo pill, patient buy-in essential, once daily dosing of long acting agents, low cost
  - Home blood pressure monitoring, more frequent HCP visits
- Consider dosing one or more agents at bedtime
- Address concerns of side effects and cost
- Discontinue interfering drugs/toxins/EtOH if possible
- Weight loss, diet (sodium reduction < 2 g/d, DASH diet, high fibre, low fat), physical activity
- Maximize blood pressure meds; emphasize thiazide or thiazide like diuretics (chlorthalidone, indapamide, HCTZ) and DHP-CCBs
- Consider addition of drugs with different mechanisms of action if standard therapy not meeting targets
  - Loop diuretics (furosemide)
    - Especially if edema, volume overload, eGFR < 30 mL/min
  - Aldosterone antagonists (spironolactone)
  - Dual CCB (amlodipine/felodipine/nifedipine + diltiazem/verapamil)
  - Alpha-blockers
  - Vasodilators (hydralazine, minoxidil) with loop diuretic/beta-blocker to offset tachycardia/edema
- Tx cause of secondary hypertension if present
- Refer to hypertension specialist (if secondary cause suspected/known; if blood pressure remains uncontrolled after >6 mo of treatment, significant intolerance/adverse effects to therapy.

Specific management of PA

a. Surgery with ipsilateral adrenalectomy should be considered for unilateral forms of hypersecretion (e.g., aldosterone-producing adenomas/unilateral adrenal hyperplasia). Patients should be followed closely after surgery as a significant proportion may remain hypertensive.
b. Mineralocorticoid receptor antagonists (particularly spironolactone in low to moderate doses) are quite effective for those with bilateral disease (e.g., idiopathic/bilateral adrenal hyperplasia).
c. Mineralocorticoid receptor antagonists should be considered for individuals who are not surgical candidates or for those who refuse surgery (even with confirmed unilateral hypersecretion). Blood pressure lowering responses to other antihypertensives (e.g., angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and calcium channel blockers) are often only modest-to-moderate. Beta-blockers are not very helpful.

References and Resources

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QI Resource 15: Thyroid Nodule

History

- History of head or neck irradiation in childhood
- Family history of thyroid cancer (first-degree relative)
- Compression symptoms (dysphagia, dysphonia, or hoarseness)
- Rate of growth
- Symptoms of thyroid dysfunction

Physical examination

- Height, weight, body mass index, blood pressure, P regular or irregular
- Palpate the neck, document the size of the nodule(s), (firm/movable)
- Check for presence of lymphadenopathy and document locations
- Assess presence of orbitopathy, lid lag, skin texture and warmth, presence of tremor
- Chest and cardiovascular examination

Investigations

- Thyroid-stimulating hormone (TSH): if normal or elevated, proceed to ultrasound; if low, obtain thyroid uptake and scan.
- Ultrasound and consider ultrasound-guided fine-needle aspiration
- Perform ultrasound (US) of the lateral neck for suspicions nodules to rule out metastatic disease.

Management

- If biopsy is not indicated, then follow with US based on size of nodules and sonographic features.
- Proceed with biopsy if indicated and manage based on results in Table 1.

Management of suspicious or malignant cytology
Preoperative imaging:
- Preoperative neck US is recommended for all patients undergoing surgery for suspicious or malignant cytology.
- Preoperative neck and chest cross sectional imaging (CT or MRI) is recommended for patients with suspected advanced disease.

Surgery:
- Indeterminate cytology nodule: lobectomy
- If molecular mutation markers are positive then proceed with thyroidectomy
- Suspicious for cancer, or >4 cm or + family history or radiation exposure: thyroidectomy
- Suspicious for cancer with metastasis (mets), extra thyroidal extension: thyroidectomy with lymph nodes dissection

≠ Molecular mutations—BRAF, RAS, RET/PTC, PAX8/PPARG mutations (if +ve 97% chance of ca)
Staging: tumor, node, metastases predicts mortality
Recurrence risk:
- Low: intrathyroidal, well differentiated, no aggressive histology, no ETE, no vascular invasion or mets, ≤5 pathologic LN micromets (<0.2 cm); minimally invasive follicular ca- capsular invasion only, non stimulated thyroglobulin (Tg) <0.2 ng/mL or TSH stimulated Tg<1 ng/mL (excellent response). Keep TSH 0.5–2. Patient may not need RAI.
- Intermediate: aggressive histology (tall cell, hobnail variant, columnar cell ca), minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2–3 cm), nonstimulated Tg ≥1 ng/mL, TSH stimulated Tg > 10 ng/mL (incomplete response). Consider RAI 30 - 70 Mci, Keep TSH 0.1–0.5
- High: gross extra thyroidal extension, incomplete tumor resection, distant mets, or involved lymph node ≥3 cm, post op Tg suggestive of mets. RAI100-200 mci, Keep TSH <0.1

Radioactive iodine (RAI):
- Low risk: older age, microscopic extrathyroidal extension, >4 cm: 0 - 30 mCi
- Intermediate risk: 30–100 mCi
- High risk: 100–200 mCi

Radioactive iodine: risks and benefits:
- Improves survival in selected high and intermediate risk patients, especially >65 and < 45 yr
- Reduces local recurrence
- Facilitate follow-up Tg easier
- S/E sialoadenitis, dental caries , slightly increased risk of secondary malignancies

Tg monitoring and TSH target:
- Non stimulated Tg <0.2 ng/mL (excellent response) and low risk—keep TSH 0.5–2 mU/L
- Non stimulated Tg ≥0.2 ng/mL (incomplete response) and low risk—keep TSH 0.1–0.5 mU/L
- Non stimulated Tg >0.2 ng/mL with TSH-stimulated Tg >10, rising Tg or Tg Ab, Keep TSH < 0.1 mU/L

Long-term follow-up:
- Annual neck US and Tg and Tg Abs levels. Use Tg guidelines above to restratify the risk of recurrence.

References and Resources

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QI Resource 16: Thyrotoxicosis/ Hyperthyroidism

Etiology/differential diagnosis

- Thyrotoxicosis associated with normal or elevated radioactive iodine uptake (RAIU):
  - Graves' disease
  - Toxic adenoma or toxic multinodular goiter
  - Trophoblastic disease
  - Thyroid-stimulating hormone (TSH) producing adenoma
  - Resistance to thyroid hormone (T3 receptor mutation)
- Thyrotoxicosis associated with near-absent RAIU:
  - Painless (silent) thyroiditis
  - Amiodarone-induced thyrotoxicosis
  - Subacute (granulomatous, de Quervain's thyroiditis)
  - Iatrogenic thyrotoxicosis
  - Factitious ingestion of thyroid hormone
  - Struma ovarii
  - Acute thyroiditis

History

- Weight loss, heat intolerance, palpitations, hyperdefecation, anxiety
- Family history of thyroid disease

Table 1
Indications for Biopsy and Follow-Up

Ultrasound features suggestive of malignancy	Indications for biopsy	Indications for follow-up if FNA is benign
High suspicion of CA (70%–90% risk)	≥1 cm	Repeat ultrasound, FNA at 6–12 mo
• Hypoechoic		
• Irregular margin		
• Taller than wide		
• Microcalcification		
• Extrathyroidal extension		
• Interrupted rim calcification		
• Soft-tissue extension		
Intermediate suspicion of CA (10%–20%)	≥1 cm	Repeat ultrasound at 12–24 mo
• Hypoechoic solid with regular margins		
Low suspicion of CA (5%–10% risk)	≥1.5 cm	
• Hyperechoic solid with regular margins		
• Partially cystic with eccentric solid areas		
Very low suspicion of CA (<3% risk)	≥2 cm	Repeat ultrasound at >24 mo
• Spongiform		
• Partially cystic, no suspicious features		
Benign	None	
• Pure cyst (<1%)		
<1 cm of any nodule	None	
Modifications		
• Hyperechoic, microcalcifications	≥ 1 cm	
• Hyperechoic, coarse calcification	1.5 cm	
• Hyperechoic , lobulated smooth margin	≥ 1.5 cm	
• Eggshell calcification	Difficult to Bx	
• Multiple nodules with low pattern of malignancy	FNA of >2-cm nodule and follow-up others	

Abbr: CA, cancer; FNA, fine-needle aspiration.

Physical examination

- Blood pressure, pulse, height, weight, BMI
- Presence of orbitopathy, tremor
- Chest and cardiovascular examination

Investigations

- TSH predominant index, Free T4, Free T3 as appropriate
- Thyroid uptake and scan
- TSH receptor Ab, CBC, LFT, 12 lead ECG

Management

- Beta-adrenergic blockade for elderly patients with symptomatic thyrotoxicosis or resting heart rates > 90 bpm or if coexistent cardiovascular disease. Consider use in all symptomatic patients. Can use atenolol 25 to 100 mg OD or bid, or propranolol 10 to 40 mg tid to qid or metoprolol 25 mg to 50 mg bid
- Graves' disease management options:
  I^{131}Therapy
    Factors favoring:
      - Females planning a pregnancy in the future (>4–6 mo)—ensure effective contraception
      - Contraindications to antithyroid drug use
    Contraindications to radioactive iodine therapy (RAI):
      - Pregnancy, lactation, individuals unable to comply with radiation safety guidelines, and females planning a pregnancy within 4–6 mo.
    Antithyroid drugs (ATD)
    Factors favoring:
      - High likelihood of remission (female patients, with mild disease, small goiters, and negative or low-titer thyroid receptor antibody [TRAb])
      - Elderly or comorbidity increasing surgical risk or limited life expectancy or unable to follow radiation safety regulations
      - Moderate to severe active Graves' ophthalmopathy
    Contraindications to ATD: previous known major adverse reactions to antithyroid drugs
    Surgery
    Factors favoring:
      - Symptomatic compression or large goiters (80g)
      - Relatively low uptake of RAI

- Females planning a pregnancy in <4–6 mo (i.e., before thyroid hormone levels would be normal if I^{131}were chosen as therapy) especially if TRAb levels are particularly high
- Patients with moderate to severe active Graves' ophthalmopathy

Contraindications for surgery:

- Substantial comorbidity

- I^{131}Therapy for Graves' disease
  - Pretreat with beta-adrenergic blockade and methimazole prior to RAI for patients at increased risk for complications due to exacerbation
  - Provide sufficient radiation as a single dose (typically 370–555 Mbq [10–15 mCi]) to render the patient hypothyroid.
  - Perform a pregnancy test within 48 h prior to treatment in any female of childbearing potential.
  - Perform thyroid function tests 1–2 mo post treatment. If the patient remains thyrotoxic, biochemical monitoring should be continued at 4- to 6-wk intervals.
  - When hyperthyroidism due to Graves' disease persists after 6 mo following I^{131} therapy, or if there is minimal response 3 mo after therapy, retreat with I^{131}
- Antithyroid drug therapy for Graves' disease
  - Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for Graves' disease, except during the first trimester of pregnancy when propylthiouracil is preferred, and in the treatment of thyroid storm.
  - Patients should be informed of side effects of antithyroid drugs and the necessity of informing the physician promptly in presence of pruritic rash, jaundice, acholic stools or dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, or pharyngitis.
  - Prior to initiating antithyroid drug therapy, perform a baseline CBC and liver profile.
  - If methimazole is chosen as the primary therapy, the medication should be continued for 12–18 mo, then tapered or discontinued if the TSH is normal at that time. If a patient becomes hyperthyroid after completing a course of methimazole, treat with RAI or thyroidectomy.
- Surgery for Graves' disease
  - Render euthyroid with methimazole preoperatively.
  - Give potassium iodide in the immediate preoperative period.
- Toxic multinodular goiter or toxic adenoma
  - Treat with either I^{131} therapy or thyroidectomy
  - Patients at increased risk of complications due to exacerbation of hyperthyroidism, including the elderly and those with cardiovascular disease or severe hyperthyroidism, should be treated with beta-blockade prior to I^{131} until euthyroid.
  - RAI can be given either as a fixed activity (approx 10–20 mCi) or an activity calculated on the basis of nodule size using 150–200 mCi I^{131}/g corrected for 24-h RAIU.
  - Check thyroid function tests 1–2 mo after I^{131} and repeat at 1- to 2-mo intervals until stable results are obtained, then at least annually
  - If hyperthyroidism persists beyond 6 mo following I^{131} therapy, retreat with I^{131}.
- Subclinical hyperthyroidism
  - TSH <0.1 mU/L: consider treatment in all individuals > 65 yr; postmenopausal women not on estrogens or bisphosphonates; patients with cardiac risk factors, heart disease, or osteoporosis; and individuals with hyperthyroid symptoms.
  - TSH < lower limit of normal but > 0.1 mU/L: consider treatment in individuals > 65 yr and in patients with cardiac disease or symptoms of hyperthyroidism
- Graves' ophthalmopathy
  - Patients with Graves' hyperthyroidism and mild active ophthalmopathy who are smokers or have other risk factors for Graves' ophthalmopathy and who choose RAI therapy should receive concurrent corticosteroids.
  - Patients with Graves' hyperthyroidism and active moderate-to-severe or sight-threatening ophthalmopathy should be treated with either methimazole or surgery.
- Thyroiditis
  - Patients with mild symptomatic subacute thyroiditis should be treated initially with beta-adrenergic-blocking drugs and NSAID's. Those failing to respond or those with moderate-to-severe symptoms should be treated with corticosteroids.
- Amiodarone-induced thyroiditis (AIT)
  - Thyroid function tests should be monitored before and at 1 and 3 mo following the initiation of amiodarone therapy, and at 3- to 6-mo intervals thereafter.
  - If hyperthyroidism occurs, distinguish type 1 (iodine-induced) from type 2 (thyroiditis) AIT.
  - Type 1 AIT tends to occur in patients with underlying thyroid autonomy in a nodular goiter, whereas type 2 AIT is due to a direct destructive effect of amiodarone on thyrocytes.
  - RAIU is occasionally measurable in type 1 AIT (particularly in regions of iodine deficiency), but not in type 2 AIT.
  - Increased vascular flow on color-flow Doppler ultrasound study may be seen in patients with type 1 AIT, but not type 2 AIT. Measurement of serum interleukin-6 levels does not reliably distinguish between the 2 types. The distinction between type 1 AIT and type 2 AIT is not always clear, and some patients have elements of both types.

- Consider stopping amiodarone in the setting of thyrotoxicosis in consultation with the cardiologist based on the presence or absence of effective alternative antiarrhythmic therapy.
- Methimazole should be used to treat type 1 AIT and corticosteroids should be used to treat type 2.
- Combined antithyroid drug and anti-inflammatory therapy should be used to treat patients with overt AIT who fail to respond to single modality therapy, and patients in whom the type of disease cannot be unequivocally determined.
- Type 1 AIT: treat with methimazole (MMI, 40 mg daily) to prevent new hormone synthesis.
- Type 2 AIT: treat with anti-inflammatory therapy such as prednisone (40 mg daily).
- When a clear distinction between type 1 AIT and type 2 AIT is not possible, a combination of prednisone and methimazole should be used.
- Thyroidectomy may be required in patients who prove refractory to medical therapy.

References and Resources

• Bahn RS, Burch HB, Cooper DS, et al. 2011 Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 21(6):593–646.

Acknowledgment

Funding was provided by The College of Physicians and Surgeons of Ontario for the development of this document.