Thyroid nodules: Background: nodules of thyroid and adrenal glands benign in 80% of cases; pituitary incidentalomas benign in ≥88% of cases

Thyroid nodules: 10 American Association of Clinical Endocrinologists guidelines — rate of cancer when detected by palpation or ultrasonography (US) 5% to 7%; rate of malignancy when lit up on positron emission tomography-computed tomography, 60%; risk for cancer increased in men, in children, in solitary nodules, and if nodule hard or central nodes palpable; if <1 cm, observe; palpable in ≥7% of population; ≥76% of women have thyroid abnormality on US; modalities for evaluation — include US, thyroid-stimulating hormone (TSH) assay, fine-needle aspiration biopsy, and radioactive iodine (RAI); US — provides information about anatomy and characteristics of thyroid and nodules; primary diagnostic modality for thyroid masses; RAI — provides information about function; not recommended unless toxic autonomous nodule (rare) suspected; indications for US — palpable abnormality; subclinical hyperthyroidism; thyroiditis; family history of thyroid disease, particularly thyroid cancer; history of exposure to radiation

Subclinical hyperthyroidism: level of TSH low, but level of circulating thyroid hormone (TH) normal; in younger patients, majority of cases due to thyroiditis; multinodular goiter possible cause; US indicated; treat if TSH <0.1 mIU/L (if 0.1-0.45 mIU/L, observe), particularly in patients ≥65 yr of age or in younger patients with symptoms; low-dose methimazole recommended; if patient tachycardic, β-blockers indicated; risk for atrial fibrillation same as that in patients with overt hyperthyroidism

Multinodular goiter: perform US and biopsy of dominant or suspicious nodules; observe with serial US and biopsy of growing nodules; >50% of enlarged thyroid nodules do not shrink on TH if TSH normal (in majority of cases, unless TSH elevated, TH does not decrease in size); treat with methimazole only if TSH <0.1 mIU/L; if level of TSH increases, rate of thyroid cancer increases

Biopsy: indications — nodule >1 cm (if <0.5 cm, observe); nodule suspicious (ie, if microcalcifications present or partially cystic; simple thyroid cysts virtually never malignant); nodule invading thyroid capsule or surrounding tissue; accuracy — false-negative rate low; rebiopsy — if nondiagnostic or suspicious

Management of solitary or dominant nodule: obtain TSH, and if normal, biopsy if nodule >1 cm (if <1 cm, observe); if elevated, probably thyroiditis, so treat as hypothyroidism (nodules disappear in ≥20% of cases) and obtain biopsy; if TSH suppressed, obtain free T4 to determine whether thyroid overactive; if free T4 elevated, obtain RAI to rule out toxic autonomous nodule

Follow-up: if nodule <1 cm in size, follow up at 1 yr (if patient concerned or history worrisome, follow up at 6 mo); no consensus on follow-up if nodule stable at 1 yr (consider annual follow-up for 5 yr)

Thyroid cancer: nonfatal in ≥98% of cases; thyroglobulin — good tumor marker for differentiated thyroid cancer; monitor annually; cannot use if antibody positive; if undetectable, follow periodically; if thyroglobulin or antibody rise rapidly, refer to oncologist; US of neck — capable of recognizing malignant central node (site of recurrence); follow-up — if patient at low risk and free of disease, maintain TSH at 0.1 to 1.5 mIU/L

Adrenal incidentalomas: nonfunctioning benign lesion in ≥80% of cases; differential diagnoses include Cushing syndrome, pheochromocytoma, adrenocortical carcinoma, metastatic lesions, and aldosteronoma; malignancy seen in ≥8% of cases; consider adrenal mass seen on metastatic survey to be metastatic lesion, not incidentaloma, unless biopsy proves otherwise; biochemical screening indicated

Indications for surgery: functioning nodules; nonfunctioning lesions >4 cm (≥3.8 cm recommended by some experts); nonfunctioning lesions <4 cm that increase in size or become hormonally active; most guidelines recommend following lesions for ≥2 yr; regular follow-up and yearly testing for hormones recommended in patients with subclinical pheochromocytoma or Cushing syndrome, with early surgery indicated if hypertension (HTN) cannot be controlled or if HTN or diabetes mellitus develops

Measurement of hormones: obtain 24-hr urine for cortisol (Cushing syndrome present if 3-4 times normal) or overnight dexamethasone-suppression test; adrenocorticotropic hormone (ACTH) low in Cushing syndrome; patients with Cushing syndrome usually symptomatic

Pheochromocytoma: obtain 24-hr urine for metanephrines or catecholamines (plasma metanephrines also beneficial; not considered pheochromocytoma if negative); 24-hr urine test has fewest false-positive and false-negative results; some pheochromocytomas nonfunctional or secrete poorly and cause subclinical disease (observe, but only as long as HTN rises rapidly, refer to oncologist; US of neck — capable of recognizing malignant central node (site of recurrence); follow-up — if patient at low risk and free of disease, maintain TSH at 0.1 to 1.5 mIU/L

Educational Objectives

The goal of this program is to improve the diagnosis and management of thyroid nodules, pituitary incidentalomas, and acute kidney injury (AKI). After hearing and assimilating this program, the clinician will be better able to:

1. Evaluate thyroid nodules using appropriate tests.
2. Recognize the indications for surgical removal of adrenal and pituitary incidentalomas.
3. Determine the appropriate preoperative preparation for pheochromocytoma.
4. Identify biomarkers that can be used in the diagnosis of AKI.
5. Prescribe appropriate fluids for volume resuscitation in cardiorenal syndrome.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. Piziak receives research support from Janssen Pharmaceuticals. Dr. Barchman reported nothing to disclose. The planning committee reported nothing to disclose.
can be controlled); malignancy rare; preoperative preparation — hydration; start α-blockade before giving β-blockers; screen for cardiomyopathy with echocardiography (present in 15%-20% of cases due to previous high-circulating catecholamines); give labetalol after α- and β-blockade

Aldosteronoma: malignancy rare; obtain serum potassium (normal in 30% of cases); measure plasma aldosterone concentration and plasma renin activity; diagnosis likely if ratio >30 and aldosterone >20 ng/dL

Biochemical testing: in 282 cases of incidental adenoma masses, diagnosed 100% of cases with Cushing syndrome and aldosteronomas and 79% of cases with pheochromocytomas; testing missed 2 small nonfunctional adrenal carcinomas, which nevertheless grow slowly and do not lead to early morbidity

Imaging: determines size and detects irregularities or necrosis in suspicious, small (<4 cm) nodules through attenuation and contrast washout

Follow-up: for subclinical disease, perform imaging annually until lesion stable (usually 1-5 yr); if in doubt, remove surgically

Pituitary incidentalomas: gland highly vascular; common site for metastasis; differential diagnoses — significant majority of primary pituitary tumors nonfunctional; if functional, frequently prolactinomas and occasionally Cushing disease; metastatic lesion; infiltrative lesions; inflammation of pituitary; mortality — low; physiologic hypertrophy — occurs in pregnancy and in hypothyroidism (due to proliferation and hypertrophy of thyrotropes); imaging — key; important to look at mass effect; if close to optic nerves or chiasm, visual field testing recommended (highly sensitive); if abnormal, surgical removal indicated; microadenomas — <1 cm; pituitary gland known to be durable (eg, in empty sella syndrome, pituitary compressed permanently, but function normal in 96% of cases); look only for hypersecretion (eg, prolactinomas, patients with acromegaly); obtain prolactin level and insulin-like growth factor 1 (IGF-1; produced by liver; stable compound; more reflective of pituitary overactivity than level of pituitary growth hormone); macroadenomas — possibly pituitary hormone deficiency and excess; obtain prolactin, IGF-1, and hormones of target organ (ie, free T4, testosterone, estradiol, or follicle-stimulating hormone) Indications for surgery: compression of optic nerves or chiasm, visual field testing recommended (highly sensitive); if abnormal, surgical removal indicated; microadenomas — <1 cm; pituitary gland known to be durable (eg, in empty sella syndrome, pituitary compressed permanently, but function normal in 96% of cases); look only for hypersecretion (eg, prolactinomas, patients with acromegaly); obtain prolactin level and insulin-like growth factor 1 (IGF-1; produced by liver; stable compound; more reflective of pituitary overactivity than level of pituitary growth hormone); macroadenomas — possibly pituitary hormone deficiency and excess; obtain prolactin, IGF-1, and hormones of target organ (ie, free T4, testosterone, estradiol, or follicle-stimulating hormone) Indications for surgery: compression of optic nerves or chiasm; hypersecretion of growth hormone or ACTH; intratable headache attributable to mass lesion

Indications for medical therapy: prolactinomas, even if abutting optic chiasm; shrink when treated with cabergoline; may require debulking in certain cases

Surgical outcomes and recommendations: ≈44% of nonfunctioning tumors cured; visual symptoms resolve in ≈80% of cases and headaches in 90% of cases; follow-up of residual pituitary tumor recommended to prevent recurrence of ocular problems; beneficial in acromegaly, prolactinomas, and ACTH-secreting tumors; removal of incidentalomas not indicated to treat migraine headaches (removal of tumor of prostate); shrink when treated with cabergoline; may require debulking in certain cases

Surgical outcomes and recommendations: ≈44% of nonfunctioning tumors cured; visual symptoms resolve in ≈80% of cases and headaches in 90% of cases; follow-up of residual pituitary tumor recommended to prevent recurrence of ocular problems; beneficial in acromegaly, prolactinomas, and ACTH-secreting tumors; removal of incidentalomas not indicated to treat migraine headaches (removal of tumor of prostate); shrink when treated with cabergoline; may require debulking in certain cases

Medical emergency: tumor may infarct and bleed into pituitary; pituitary obliterated due to confined space, which causes acute hypopituitarism; treat for secondary adrenal insufficiency; patients often present late for neurosurgical decompression

Acromegaly: tumor grows slowly and causes enlargement of sella; characteristics include “square” hands, large lips, and spaces between teeth
Disadvantages: necessitates choosing appropriate form and determining cutoff level for specific problem

**Interleukin-18:** inflammatory cytokine; elevated by caspase 1 and injured proximal tubule cells; animal studies suggest that ischemic injury in heart, brain, or kidneys increase level; urine level increased in ATN, compared with prerenal disease, urinary tract infection and CKD; significantly elevated in patients undergoing renal transplantation, and may predict delayed graft function

**Urine N-acetylglucosaminidase:** marker for proximal tubular injury; urinary secretion increased in AKI, differentiating it from CKD; may differentiate AKI from other causes of elevated creatinine; not used because assay complicated and costly

**Cardiorenal syndrome:** decompensated heart failure — reduce afterload and promote diuresis; NGAL with brain natriuretic peptide may be highly beneficial in determining point at which diuresis must be stopped to avoid risk for kidney failure; levels of NGAL signaling impending AKI lower in this population

**Fluids for volume resuscitation:** saline increases blood pressure because it remains in arterioles, but acid effect may decrease tissue perfusion by “clamping down” peripheral capillary beds; normal saline (NS) — has strong ion difference (SID) of 0 (SID used to evaluate acid-base status; normal SID ≈ 40); aggravates tendency for hyperchloremic acidosis; lactated Ringer’s solution preferred; isotonic solution of balanced electrolytes in water (Normosol-R) — more physiologic, with SID and pH closer to normal; NaCl replaced at expense of bicarbonate, with resulting hyperchloremic acidosis; preliminary studies show increase in urine NGAL and cystatin C with administration of NS, compared with other more physiologic solutions; cytokine production, inflammation, and free-radical formation increase with hyperchloremic acidosis

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**Suggested Readings**


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**Estimated time to complete the educational process:**

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes

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THYROID NODULES AND ENDOCRINE INCIDENTALOMAS/ACUTE KIDNEY INJURY

1. In a patient who presents with a thyroid nodule, there is a greater likelihood of malignancy if:
   1. The patient is female
   2. The patient is a child
   3. Central nodes are palpable
   4. The nodule is solitary and hard
   (A) 1,3 (B) 2,3 (C) 1,2,3 (D) 2,3,4 **

2. Which of the following is the primary diagnostic modality for thyroid masses?
   (A) Ultrasonography ** (C) Radioactive iodine
   (B) Thyroid-stimulating hormone (TSH) assay (D) Fine-needle aspiration biopsy

3. Subclinical hyperthyroidism is characterized by _____ levels of TSH and _____ levels of circulating thyroid hormone.
   (A) High; low (C) High; normal
   (B) Low; low (D) Low; normal **

4. A cortisol reading 3 to 4 times normal on 24-hr urine test is associated with:
   (A) Adrenocorticoid carcinoma (C) Pheochromocytoma
   (B) Aldosteronoma (D) Cushing syndrome **

5. Surgery for pituitary incidentalomas is indicated in all the following cases, except:
   (A) Compression of optic nerves or chiasm
   (B) Hypersecretion of growth hormone or adrenocorticotropic hormone
   (C) Intractable headache attributable to mass lesion
   (D) Prolactinoma abutting optic chiasm

For questions 6-9, match the biomarkers in Column I with the corresponding characteristic in Column II.

<table>
<thead>
<tr>
<th>Column I</th>
<th>Column II</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Cystatin C</td>
<td>(A) Significantly elevated in patients undergoing renal transplantation and may predict delayed graft function</td>
</tr>
<tr>
<td>7. Kidney injury molecule-1</td>
<td>(B) Surrogate for glomerular filtration rate, but not true marker of acute kidney injury unless present in urine</td>
</tr>
<tr>
<td>8. Neutrophil gelatinase-associated lipocalin (NGAL)</td>
<td>(C) Iron chelator that acts as an antimicrobial</td>
</tr>
<tr>
<td>9. Interleukin-18</td>
<td>(D) Transmembrane receptor that is upregulated to high levels in the proximal tubule after ischemic and nephrotoxic injury</td>
</tr>
<tr>
<td>10. NGAL with _____ may be useful in determining the point at which diuresis must be stopped to avoid risk for kidney failure in cardiorenal syndrome.</td>
<td>(A) Cystatin C (C) Brain natriuretic peptide</td>
</tr>
<tr>
<td></td>
<td>(B) Creatinine (D) Interleukin-18</td>
</tr>
</tbody>
</table>

Answers to Audio Digest Internal Medicine Volume 61, Issue 41: 1-A, 2-B, 3-A, 4-A, 5-D, 6-B, 7-C, 8-A, 9-A, 10-B